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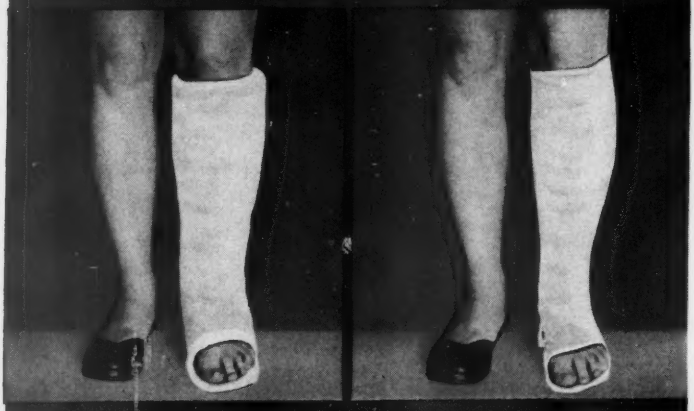

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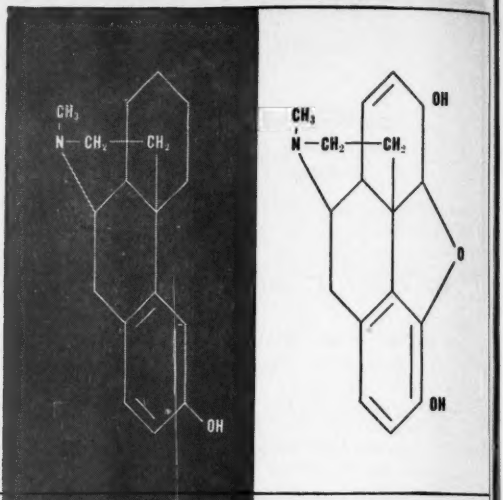

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FOREWORD

Baylor University was chartered by the Republic of Texas in 1845, being the first university in the state. In 1886 it was rechartered, placed under the control of the Baptist General Convention of Texas and located at Waco, in consolidation with Waco University.

In 1903 the Board of Trustees of Baylor University assumed limited responsibility for the Medical Department, which had been organized in Dallas in 1900 and was known as the Medical Department of the University of Dallas. This agreement with Baylor University was for a term of three years, at the end of which period of time the arrangement was renewed for three years. At the conclusion of this arrangement, in 1909, Baylor University assumed absolute responsibility for its Medical Department, which action converted the Baylor University College of Medicine into an integral and co-ordinate part of the University.

The college operated continuously in Dallas until the early summer of 1943 when it was removed to Houston to become the College of Medicine of the then projected Texas Medical Center. The first session opened July 12, 1943, with the laboratory departments, the library and administrative offices housed in quarters formerly occupied as a retail store by Sears Roebuck Company. These quarters were occupied until the fall of 1947 when the college was moved to its permanent home, the Roy and Lillie Cullen Building, on a 17.5 acre campus in the heart of the Texas Medical Center. The College of Medicine was the first unit to be established in the Medical Center which is growing rapidly in facilities.

The Center is being developed by grouping some existing medical organizations and some newly conceived ones around education and research facilities in a small geographic area. Provisions of this arrangement call for close collaboration and cooperation of the various constituent units and a minimum of reduplication of effort. Such co-ordination of professional and scientific endeavor is under the guidance of a Medical Center Director appointed by the Medical Center Board of Trustees.

Baylor University College of Medicine enjoys a central location among the other institutions. It is adjacent to the now-building University of Texas School of Dentistry on the one side, and the now-building Houston Academy of Medicine Library on another. It will have adjoining corridors with the soon to be built Jefferson Davis (City-County) Hospital. The Medical School is affiliated with this hospital by contract and makes it the center of its clinical teaching program. Baylor also enjoys affiliation with the Methodist Hospital, in the Texas Medical Center, and the Veterans Administration Hospital which is situated only a stone's throw from the Medical Center boundary. Other types of working arrangements exist between Baylor and various medical facilities, in and out of the center.

Ever mindful of its responsibilites and functions—education, research and community services—the College of Medicine has made great strides in the fulfillment of these during the nine years it has been in Houston. The Department of Surgery has kept well apace with this development and progress.

WALTER H. MOURSUND, M.D.
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TRACHEO-ESOPHAGEAL FISTULA DUE TO NONPENETRATING INJURY*

M. E. De Bakey, M.D.
John P. Heaney, M.D.

Houston

Trauma is a rare cause of tracheo-esophageal fistula. Most acquired fistulas between the esophagus and tracheobronchial tree develop as the result of neoplasm or infection.[1, 29, 40, 41, 42, 58] In the collected series of 456 cases of acquired tracheo-esophageal fistula, Mangaveira-Albernaz found that 80 per cent were caused by neoplasm, 8 per cent by inflammatory disease and 9 per cent by trauma. More recently, Coleman and Bunch in an analysis of 75 collected cases of acquired nonmalignant tracheo-esophageal fistulas found that 21 (28 per cent) were caused by trauma and of these only 4 (5.3 per cent) were due to nonpenetrating injury. Of those due to trauma an appreciable number occur after chemical injury, its subsequent endoscopic treatment, or both.[1, 12, 15, 22, 29, 52] Such fistulas are much less common, however, than uncomplicated periesophageal infection without fistula.[56] Reports concerned with external injury to thoracic structures generally or to the esophagus or trachea specifically, including data compiled from World Wars I and II, emphasize how infrequently lesions of the esophagus and trachea or large bronchi are seen clinically.[4, 10, 15, 29, 32, 38, 42, 44, 60, 61]

The supposition that many more injuries of the esophagus and major air passages do occur from penetrating fragments and terminate fatally, is easy to accept in view of the proximity of large vessels which might be simultaneously lacerated. Lesions of the esophagus or major air passages may also occur as a result of nonpenetrating blows upon the surface of the body.[2, 4, 11, 15, 21, 32, 42, 44, 45, 48, 61, 65] Rarely in such injuries both the alimentary and respiratory tubes are damaged in such a fashion that an esophago-respiratory fistula develops.[2, 3, 11, 42, 48, 49, 61, 65] Herewith is presented a report of a case in which an unusually large tracheo-esophageal fistula followed an external injury not associated with fracture of the bony thoracic framework.

CASE REPORT

A white man, aged 22 years, was in an automobile accident on Nov. 23, 1949, being thrown against the steering wheel and thence through the windshield. Further details of the accident are uncertain, inasmuch as he temporarily lost consciousness. A shadow in the right lower pulmonary field was apparent on the second day after injury and was interpreted as pneumonia. Subcutaneous cervical and thoracic emphysema soon appeared and became progressive. On the seventeenth day he was transferred, in acute respiratory distress, to the Veterans Administration Hospital in Salt Lake City, Utah. There was pronounced subcutaneous emphysema over the face, neck, both upper extremities and anterior torso down to the inguinal region.

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* From the Department of Surgery, Baylor University College of Medicine and The Veterans Administration Hospital, Houston, Texas.

A roentgenogram of the chest revealed bilateral, complete pulmonary expansion without pneumothorax. Further, there was no demonstrable mediastinal emphysema. Because of the great quantity of subcutaneous air, bilateral supraclavicular incisions were made through the skin and subcutaneous tissues, to permit release of air presumed to be under tension.

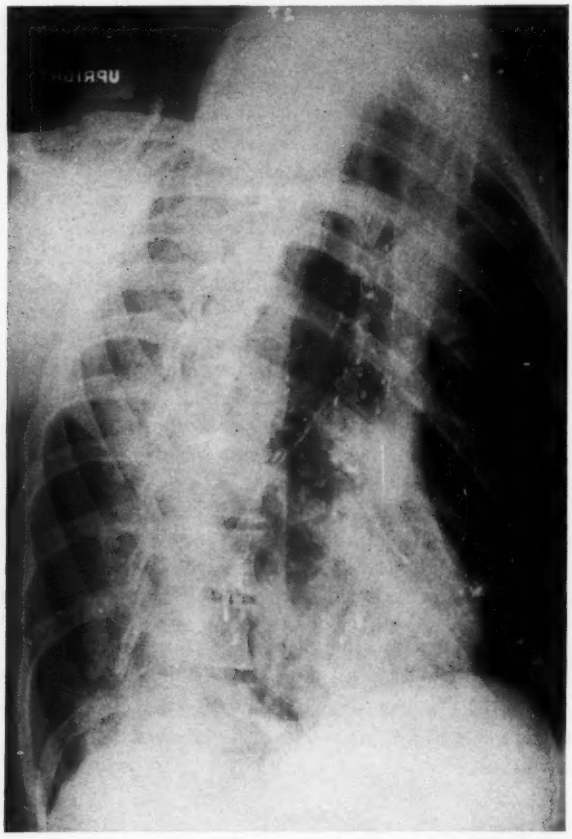

FIG. 1. Roentgenogram of chest following instillation of lipiodol in trachea showing linear tracheo-esophageal fistula extending from about 5 cm. above bifurcation to about 1 cm. below bifurcation in left main bronchus.

The following day, for the first time, the patient experienced violent coughing paroxysms on swallowing. A diagnosis of tracheo-esophageal fistula was therefore established clinically. Three days later this was confirmed by oral ingestion of lipiodol, which clearly outlined both the esophagus and tracheobronchial tree. A Levine tube was inserted into the stomach for feeding purposes.

Ten days after admission to the Utah Veterans Administration Hospital, bronchoscopy was performed and the fistula cauterized. Because it was thought that the Levine tube might cause esophageal irritation, jejunostomy was done the following day. Interestingly, al-

though the patient had no signs of pneumothorax on admission, complete left pneumothorax developed some time between December 15 and December 22. This was not appreciated

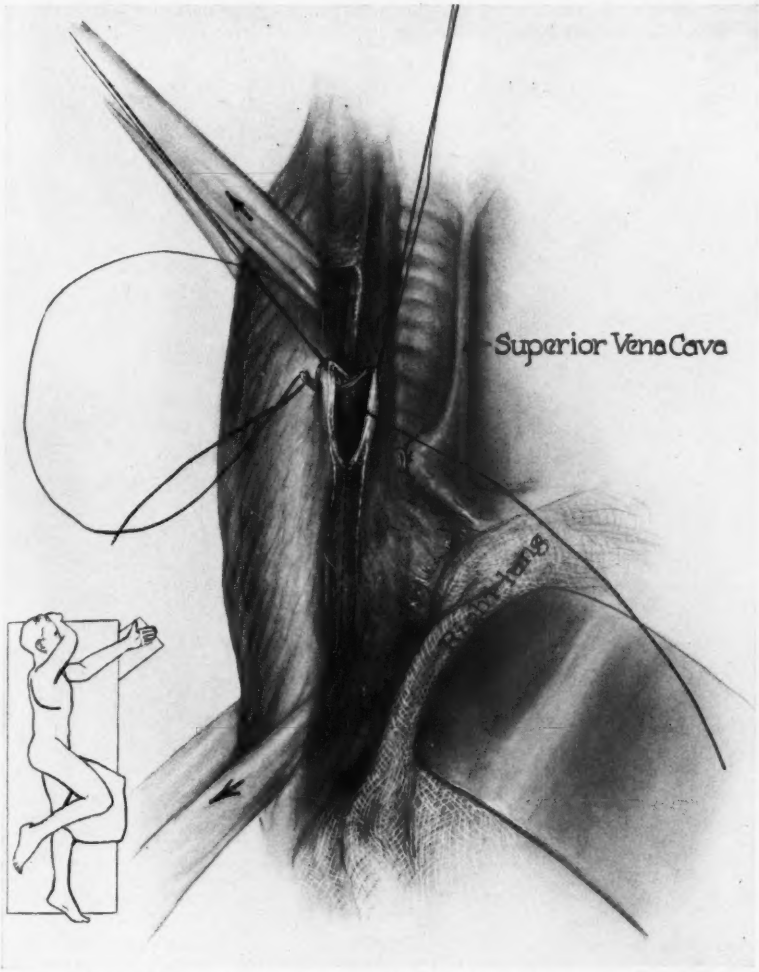

FIG. 2. Drawing showing tracheo-esophageal fistula found at operation. Inset shows patient in left lateral position and line of incision for approach through right hemithorax. The right lung has been retracted downward and forward, the mediastinal pleura opened, the azygos vein divided between ligatures, and the esophagus freed above and below fistula with tapes applied for traction. The fistula which has been opened at its upper end lies between the membranous portion of the trachea and left main bronchus and the adjacent anterior wall of the esophagus.

clinically but was demonstrated roentgenographically on the latter date. Thoracentesis performed twice brought about re-expansion. Bronchoscopy with cauterization of the fistula which was repeated on Jan. 12, 1950, showed severe suppurative bronchitis. The course in

the hospital was essentially afebrile. The patient left without medical permission on Jan. 18, 1950.

He travelled by bus from Salt Lake City to Houston, Texas. On the trip, all nourishment had been taken by mouth. He had learned by assuming certain positions and by timing of swallowing to ingest food without undue difficulty. Incidentally, he had gained weight during the week of the trip.

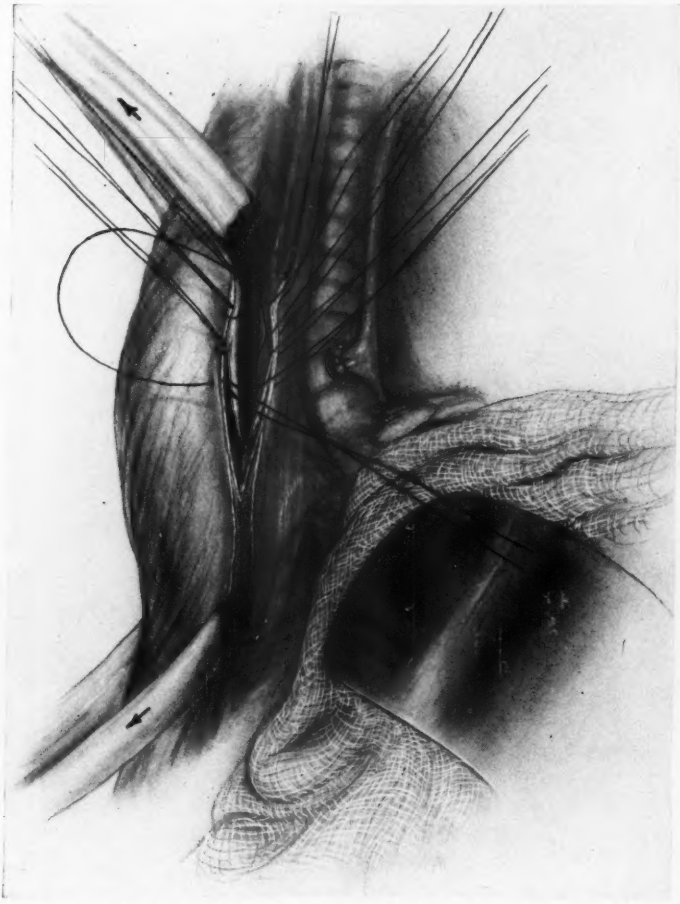

FIG. 3. Drawing showing technic of closure of fistula, segment by segment. Interrupted fine silk sutures are used to repair the opening which in the esophagus are placed so that the knots lie in the lumen.

The patient was admitted to the Veterans Administration in Houston, Texas, Jan. 25, 1950. Examination revealed expiratory rales over both pulmonary fields and moist rales at both bases. Bilateral supraclavicular scars and a healed left upper rectus abdominal incision were apparent. A jejunostomy catheter protruded from a small incision in the left upper quadrant of the abdomen.

A roentgenogram of the chest revealed prominent bronchovascular markings, especially on the right, and an area of increased density in the right pericardiac region which was interpreted as pleural thickening. Bronchoscopic examination showed an elongated, linear communication between the posterior wall of the lower trachea and esophagus. The long axis of the aperture was longitudinal. Purulent secretion was present in the basilar bronchi,

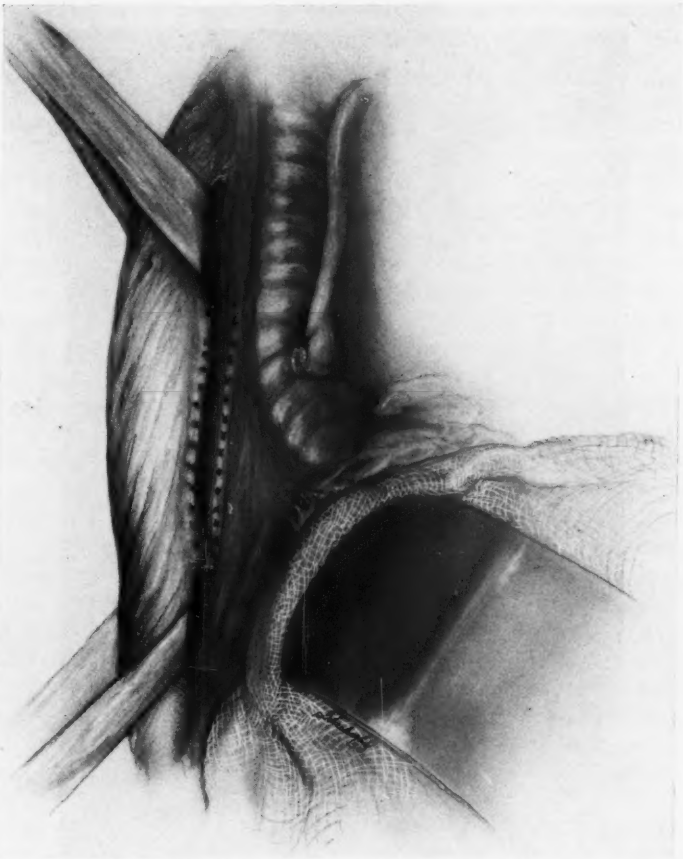

FIG. 4. Drawing showing technic of repair of fistula. The first row of sutures are reinforced with a second row of interrupted fine silk sutures and the repair completed by approximating the overlying mediastinal pleura.

bilaterally. Four days after this admission, bronchograms, following instillation of lipiodol into the tracheobronchial tree, demonstrated clearly the outline of both the esophagus and the bronchial tree (fig. 1).

On Feb. 9, 1950 thoracotomy was done. The right pleural cavity was entered through the bed of the fifth rib. The upper lobe was adherent in the apex by multiple, filmy adhesions. Its mediastinal surface was densely adherent to adjacent structures. Cleavage planes in the upper part of the mediastinum were partially obliterated; the area was exceedingly vascu-

lar. The azygos vein was divided. The fistula was readily identified between the esophagus posteriorly and the trachea and left main stem bronchus anteriorly. It measured 6 cm. in length and extended from a point 5 cm. above the carina, downward and slightly to the left. The well of the fistula was composed only of the mucosal stratum, supported by adjacent areolar tissue. The esophagus was hypertrophied and dilated; it ballooned out with each expiration.

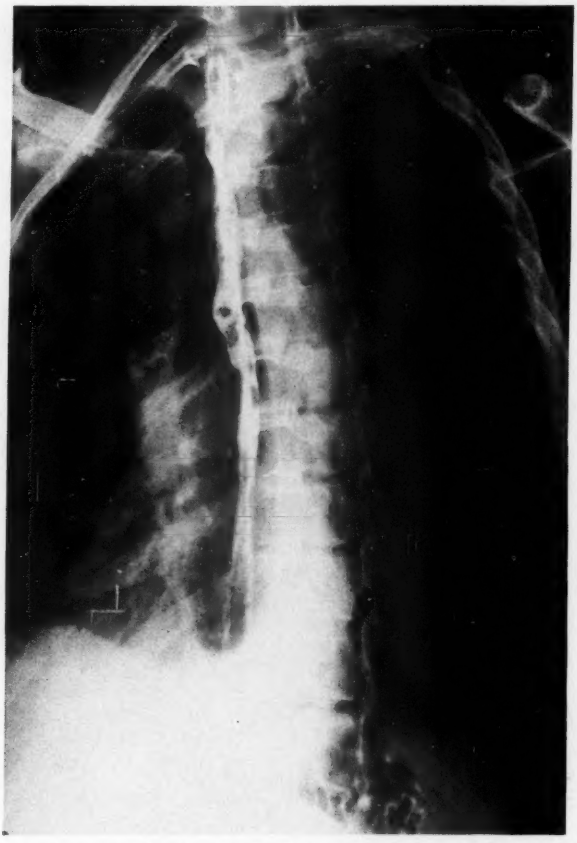

FIG. 5. Roentgenogram taken on the twelfth postoperative day following ingestion of lipiodol showing normal relationship of esophagus and the more translucent trachea and left main bronchus anteriorly.

After the involved esophageal and tracheobronchial elements had been isolated permitting definition of the fistula, the latter was divided from above downward, a short distance at a time (fig. 2). The esophageal and tracheal openings so created were closed step by step as downward division of the fistula was carried out (fig. 3). Thus, the process of obliteration was completed without widely opening either the esophagus or the trachea and without significant compromise of the positive pressure control maintained by the anesthesiologist. Each of the esophageal and tracheobronchial suture lines was reinforced by a second

layer of interrupted silk sutures (fig. 4). The tracheal repair was further reinforced by attachment of adjacent mediastinal pleura.

A thin rectangular piece of gelfoam was placed between the esophagus and trachea, further separating the two suture lines. An intercostal catheter was inserted for water seal drainage following which the thoracic wall was closed anatomically with interrupted silk for all layers.

Feedings were allowed on the second postoperative day and increased gradually. The incision healed per primum.

On the twelfth postoperative day, endoscopic and roentgenographic studies following instillation of lipiodol showed satisfactory closure of the fistula (fig. 5). The jejunostomy tube, which had not been used by which had been retained as a safety valve, was removed on the fifteenth postoperative day. The patient was discharged three days later.

COMMENT

Six cases of patients (including our own) with tracheo-esophageal fistulas as the result of nonpenetrating trauma have been reported during the past 15 years. Four of these have appeared within the past five years. This apparent increase in incidence may be due to the hazards of advancing mechanization or may be the result of improved first aid treatment of patients with thoracic injuries. It is noteworthy, too, that in the latter 4 cases, symptoms were relieved by surgical closure of the fistula.

The condition of the patients when first seen varied considerably. In the case reported by Albi and Gilchrist, the patient was alert and cooperative and the vital signs and blood pressure were normal. The only evidence of external thoracic injury was the presence of tenderness over the upper portion of the left side of the chest. In the case described by Stephens and Ferrier,[61] the patient had a fractured scapula but no other evidence of thoracic injury; he was unconscious for 12 hours, presumably because of an associated skull injury. The patient described by Adams and Malvey,[2] was in a state of shock; the only evidence of external thoracic injury was the presence of an abrasion at the second interspace at the left sternal border. The exact status following injury in our case and that reported by Vinson[65] is not known. Neither had reported roentgenographic evidence of thoracic injury. Only Piquet's patient had fractured ribs with evident compression of the thorax.[49] According to Simeone and associates,[56] early shock is not generally characteristic of the *crush syndrome*: however, in only 2 of the cases reported by him were there thoracic injuries.

Evidence of intrathoracic injury may also be meager. In the case of Albi and Gilchrist,[3] only hemoptysis combined with negative nasopharyngeal signs pointed to pulmonary damage. The roentgenograms of the chest showed no abnormality. In other instances, emphysema of the neck and face were present[2] or the patient suffered from severe substernal pain.[65] Our patient showed early right lower lobe pneumonia, probably the result of pulmonary parenchymal contusion and ecchymosis. None of the 6 patients had early pneumothorax though it developed unilaterally after three weeks in the case herein reported.

The fistula may develop immediately as in the case of Adams and Malvey[2] or may not appear for several hours or several days.[3, 47, 61, 65] In our case, the diagnosis was first suspected approximately two and one-half weeks following the

accident. One wonders whether it might have been present before this. Stephens and Ferrier[61] commented about the possible life-saving effect in delay of development of the fistula in that mediastinitis might have been averted by agglutination of the esophageal and tracheal walls. Whereas that is an inviting supposition, one cannot be sure that the esophagus or trachea, or both, have not ruptured into the mediastinum prior to erosion of the other to produce focal mediastinitis, which may have been controlled as a result of antibiotic therapy. In Vinson's patient, mediastinitis was seen at autopsy two weeks after injury.

The fistula in each instance developed between the lower trachea and esophagus or the right or more often the left main stem bronchus and esophagus. In Stephens and Ferrier's[61] case, as in ours, it extended downward toward the left main bronchus. The actual length of the fistulas varied from 1 cm.[3] to 6 cm. (authors' case). In each instance too, the communication was linear in nature. These are fairly characteristic features of the site and nature of the fistulas and are perhaps best explained by the anatomic relationship of the trachea and esophagus in this region.

Once the fistula is established the most characteristic manifestation is the occurrence of a sudden strangling sensation with severe paroxysms of coughing almost immediately after swallowing food or fluids. There is usually a definite pause of a few seconds between the act of deglutition and the occurrence of this manifestation and the ingested material may be coughed up during the paroxysm. Sometimes, as in our case, the patient may learn that by swallowing when he is in certain positions, usually recumbent, this strangulating sensation may be avoided.

These characteristic symptoms are almost pathognomonic of a tracheo-esophageal fistula and should readily lead to the diagnosis which can easily be established by roentgenographic studies following the instillation of iodized oil in the trachea demonstrating the communication with the esophagus. Additional information concerning the site, extent and nature of the fistula may be obtained by bronchoscopy and esophagoscopy which also permit the biopsy specimen of tissue if this seems indicated.

Treatment depends upon the cause and nature of the fistula. In some instances particularly in small fistulas caused by nonspecific inflammation, closure has been accomplished by chemotherapy and local cauterization. Surgical intervention, however, with anatomic repair of the opening in the esophagus and trachea is considered the procedure of choice in the most extensive type such as reported herein. Four cases of this type including our own have been successfully repaired in this manner. In all of these cases the approach has been much the same as that described and illustrated in our case.

SUMMARY

An unusual instance of acquired tracheo-esophageal fistula resulting from nonpenetrating injury successfully repaired surgically is reported. A review of the literature reveals these lesions to be relatively rare, there being only 5 previously reported cases, only 3 of which were repaired surgically. Surgical man-

agement consists essentially in division of the fistula through a transpleural approach from the right and closure of the esophageal and tracheal openings in two layers with interrupted silk sutures.

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THE INFLUENCE OF ANTIBIOTICS ON THE PRODUCTION AND RECOGNITION OF INFECTIONS*

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The availability of antimicrobial agents effective against most of the pathogenic bacteria, rickettsias and large viruses has made it even more important to establish etiological diagnoses in both local and systemic infections. It is often necessary, however, to begin therapy prior to an exact laboratory diagnosis and on the basis of the clinical impression of the most likely etiologic agent. In the past this clinical impression has been based on a careful evaluation of the history of the epidemiology and development of the infection as well as the findings on examination of the patient. The widespread general use of antibiotics in the prevention and treatment of infection and the frequency of previous antibiotic therapy in an individual patient has made a consideration of the influence of antibiotics on the cause of the infection an important factor in arriving at the most likely etiologic agent. It is the purpose of the paper to present illustrations of some of the influence of antibiotics on systemic diseases and infections complicating other illnesses. Awareness of these changes made by the antibiotics in the natural history of infections may aid in establishing a more accurate clinical diagnosis.

Influence of Antibiotic Therapy on the Etiologic Probabilities. A careful history of the previous antibiotics received by a patient with particular reference to the onset of the infection, may provide valuable clues helpful in determining the most likely etiologic agent. If a patient receives an antimicrobial agent at the time the infection develops, such as during routine preoperative or postoperative therapy, the etiologic agent is not likely to be in the group of microorganisms ordinarily inhibited by the agent being administered. If a patient develops an infection while receiving penicillin, for example, hemolytic streptococci, pneumococci, and gonococci can almost entirely be excluded as etiologic possibilities. The development of infections during streptomycin therapy tends to eliminate most of the gram negative bacilli as possibilities. This is particularly true if the patient is receiving his first course of streptomycin. The rapid development of resistance of all bacteria to streptomycin makes this less helpful in those patients having had the drug administered previously. If either aureomycin, terramycin, or chloromycetin is being administered most of the bacteria can be eliminated as causes of the infection, except for Proteus, Pseudomonas, and Aerobacter aerogenes. Staphylococcal infections may develop during therapy with any of the antibiotics (see case 1).

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The administration of an antibiotic a short time before the development of an infection usually means that the etiologic agent is in the group not susceptible to the specific antibiotic. Similarly, if repeated courses of antibiotics have been given the etiologic agent is likely to be a resistant microorganism.

Many patients have already been given therapeutic trials with one or more of the antibiotics when they are admitted to the hospital for the treatment of an infection. If a patient fails to respond to an adequate trial of an antibiotic it usually means that the etiologic agent is not in that group of microorganism responding to that particular agent. It is difficult to determine what constitutes an adequate trial in some cases, but if a drug is given according to the usual recommended doses and according to the usual recommended route there is likely to be some evidence of improvement within 48 hours after beginning therapy. There are a few outstanding exceptions to this, namely infections due to Brucella, Salmonella, and Pasteurella tularensis, in which the clinical response may be on the fourth or fifth day of therapy. Generally speaking, the time interval between the beginning of the administration of a bactericidal drug and the clinical response is shorter than that following the use of a bacteriostatic drug.

It is too often assumed that the failure of response is due to the inadequate size of dose and larger doses of the same drug are given before another approach to the problem is considered. There are cases in which an infection will not respond to the usual doses and will respond to larger doses, but these are special problems in themselves and do not represent the usual reaction. Infections may under certain circumstances be due to sensitive microorganisms and not respond because of failure of the antibiotic to reach the actual infection, or more commonly, the failure to drain adequately a localized infection.

The diagnosis of many of the classical infections has been made on the basis of the consistency of the clinical manifestations and course of infections. Antibiotics have made this more difficult in some cases, in that the clinical course and usual diagnostic procedures may be altered without actually aiding materially in the suppression of the infection. It may be difficult to obtain positive blood, stool, or urine cultures in a patient with typhoid fever if he is receiving terramycin, but his clinical course is not likely to be changed by this drug. On the other hand, if a patient with typhoid fever is given chloromycetin for an insufficient period of time, he may develop a chronic bacteremia when the drug is discontinued. The development of a skin rash due to hypersensitivity to an antibiotic may confuse the clinical picture of an infection.

The Influence of Previous Antibiotic Therapy on the Prediction Clinically of Sensitivity of Etiologic Agent to the Various Antibiotics. It is important to attempt to predict clinically not only the most likely etiologic agent, but also the sensitivity of the particular strain involved to the various antibiotics in order that the most effective drug may be used promptly. One of the fundamental maxims in management of infections is that *if an infection develops in the presence of therapy with an antibiotic, the etiologic agent is likely to be resistant to the agent being administered* (see case 1). There are exceptions to this, but they are rare. Although one suspects or has proved that the etiologic agent responsible for the infection

under consideration is ordinarily sensitive to penicillin and the infection develops during routine postoperative penicillin and streptomycin administration, one can conclude with reasonable certainty that the particular strain is resistant to both penicillin and streptomycin.

One may also receive help in the prediction of the sensitivity of the causative agent from the history of the previous antibiotic therapy. If a patient has received one drug repeatedly prior to the development of an infection, the etiologic agent is likely to be resistant to the drug previously given. If a relapse occurs after adequate dose and duration of a drug, it frequently means that the etiologic organism has become resistant. Exceptions to this exist in the case of walled-off infections, infections in nonviable tissue, or in those infections in which the organisms live intracellularly.

A knowledge of the usual sensitivity of a becterial species may be of value in anticipating the result of the sensitivity tests. Streptococcus faecalis is almost always relatively resistant to penicillin and streptomycin, whereas hemolytic streptococcic are quite sensitive to penicillin. Pseudomonas aeruginosa is usually resistant to aureomycin and chloromycetin, but always sensitive to polymyxin B. Bacillus proteus is usually resistant to most of the antibiotics, but an occasional strain is sensitive to streptomycin, unless the patient has been given streptomycin within recent weeks.

Information regarding the source of the infection and the location of the patient at the time the infection was contracted may be of value in predicting the sensitivity of the etiologic agent. This is particularly helpful in staphylococcal infections. About 15 per cent of the staphylococci isolated from patients at home or in the office are resistant to penicillin, but about 70 per cent of the strains isolated from infections developed in the hospital are penicillin-resistant. In one case penicillin therapy provides a reasonable chance of improvement, but in the other it would be hazardous to rely on penicillin alone.

The Influence of Antibiotics on Postoperative Systemic Infections. The routine use of antibiotics before and after surgical procedures has decreased markedly the incidence of wound infections and postoperative pulmonary infections. The decreasing frequency of these infections has tended to emphasize the less frequent but even more important systemic infections that may develop as a complication of surgery. It is well known that following dental surgery, a transient bacteremia occurs in a high percentage of patients. Ordinarily this is of no clinical significance but occasionally the bacteria may persist in the blood stream or may be localized in some distant organ. Because of high incidence of the development of bacterial endocarditis following such procedures it is now generally the practice to administer penicillin prophylactically in patients with pre-existing heart disease requiring dental manipulation.

The frequency of transient bacteremias following surgery of the urinary tract has also been recognized.[2] Chills and fever following transuretheral prostatic resections are common, but usually of little significance unless the bacteremia is due to an organism resistant to the drugs being used for antibacterial coverage. The importance of blood stream infections following urinary tract surgery in the

development of subacute bacterial endocarditis has not been generally recognized. In Houston, during the past two years, 4 cases of subacute bacterial endocarditis following urological surgery and 1 case following a currettage for an incomplete abortion have been observed (see case 2). The incidence of heart disease of some type in urologic practice is so common that prophylactic penicillin therapy should be used routinely before and after manipulation of the urinary tract. Doses of penicillin larger than the usual prophylactic dose are necessary since the relatively resistant enterococcus is a frequent inhabitant of the genitourinary tract. Surgical manipulation in any infected field is potentially a source of a blood stream infection and its complications. Systemic or metastatic infections should be considered as possible causes of the fever in patients having persistent temperature elevations following such operations.

Superimposed Infections During Antibiotic Therapy. There are two general types of infections that might develop during antibiotic therapy. The most common is due simply to the survival of resistant strains of bacteria when an infection is due to more than one microorganism. An antibiotic may suppress the strain which is predominant, but allow another to multiply and assume the major role in the pathologic process. This occurs frequently in wound infections, due either originally to several microorganisms or being contaminated from the exposure to the air. It may also occur in infections of the lung, intestinal tract, skin, or body cavity communicating with the exterior, such as empyema associated with a bronchopleural fistula. Organisms resistant to the antibiotic being administered almost always eventually develop in infections of this type so that if surgery is contemplated it should be planned before this takes place.

The second type of infection that may develop during antibiotic therapy is due to the same principle of the naturally occurring bacterial antagonisms that lead to the development of antibiotics. As early as 1877, Pasteur demonstrated that certain bacteria occurring in nature possessed an antagonistic effect on other microorganisms. This lead to the treatment of infections by the inhibition of the causative organisms by adding a mixed culture of bacteria, filtrates of cultures, and ultimately the purified antagonistic principle. An antibiotic, then, attempts to suppress pathogenic organisms that might be present in some part of the body that is normally sterile or to inhibit some normal bacterial inhabitant of the body that might be producing an inflammatory reaction because of its ability to become more prominent or more virulent than normally. Likewise an antibiotic may contribute to the development of an infection by removing some of the normally occurring antagonistic microorganisms, allowing another organism to grow without opposition. This alteration may be accomplished by changing the normal flora in such a way as to raise or lower the pH, oxygen concentration, changes in the nutritional substances, or specific growth enzymes, stimulating the growth of some organisms and inhibiting others. There are many examples of this type of infection resulting from antibiotic therapy. Monilial infections of the gastrointestinal, respiratory, and genital tract commonly develop during the administration of antibiotics. Proteus and Pseudomonas infections have been observed to develop during therapy with aureomycin, chloromycetin, and terra-

mycin. Serious staphylococcal infections have occasionally developed during terramycin therapy.[3]

Superimposed infections are most likely to develop if there is some interference with the host's resistance to infection. This may be due to decrease in general immunity, such as in blood dyscrasias, diabetes, advanced liver diseases, or nutritional deficiencies. Patients with leukemia, for example, frequently develop Pseudomonas septicemia as the terminal illness during antibiotic therapy. During treatment for one kind of pneumonia, a cirrhotic may develop an acute pneumonia due to another etiologic agent.

There may be local interference in the body's defense mechanisms. Of particular interest in surgical conditions is the importance of adequately draining localized infections and removing nonviable tissue. It is a common experience for a urinary tract infection associated with obstruction to recur with different etiology while still being treated with the antibiotic originally causing a remission of the symptoms of the infection. One should suspect, then, a superimposed infection if a patient at first responds to an antibiotic and then develops evidence of renewed infection, particularly if there is reason to believe that there is some interference in the host's resistance to infection (see case 3).[1, 4]

CASE REPORTS

Case 1. A 24 year old white man was admitted to the hospital because of acute poliomyelitis. His illness began three days previously and at the time of admission he had paralysis of his legs. Forty-eight hours later he was completely paralyzed and was placed in a tank respirator. On the third hospital day a tracheotomy was performed and from the third to the fifteenth hospital day the patient did well except for a slowly rising temperature.

On the fifteenth hospital day signs of severe cerebral anoxia were noted and the airway seemed obstructed. Bronchoscopy was performed and large quantities of thick sputum were aspirated from the major bronchi. The entire tracheo-bronchial tree was involved by an acute purulent bronchitis. The patient at first improved but bronchoscopy became necessary frequently and large amounts of purulent material were continually aspirated from the trachea.

Roentgenograms of the chest on the fourteenth, nineteenth, and twenty-sixth hospital days demonstrated only an increase in the bronchovascular markings.

The patient's temperature continued to rise notwithstanding adequate therapy with most of the antibiotics. On the thirtieth hospital day, the case was reviewed, paying particular attention to the previous antibiotic therapy. It was suggested that a resistant strain of staphylococcus was most likely the etiological agent and that to increase the doses of a previously administered antibiotic would not benefit the patient. Erythromycin was therefore started in the dose of 500 mg. every six hours. Cultures of the bronchial exudate taken just before beginning the antibiotic revealed a pure culture of Staphylococcus albus. It was resistant in vitro to all the previously employed antibiotics, but its growth was inhibited by one microgram per milliliter of erythromycin.

The patient improved as indicated by the decrease in temperature and the white blood cell count presented in figure 1. However, on the forty-fourth hospital day the patient died from peripheral circulatory collapse which followed a brief period of obstructed breathing and cyanosis and a terminal rise in temperature.

Case 2. A 62 year old man had a cystectomy and ureterosigmoidostomy on Sept. 10, 1951 because of carcinoma of the bladder. He had been well previously except for a history of rheumatic fever since 1933. His postoperative course was complicated by acute pyelonephritis which improved following a course of terramycin. He continued to run a low grade

fever not withstanding the administration of sulfisoxazole, penicillin, streptomycin, aureomycin, chloramphenicol, terramycin, and polymyxin B. During the next few months he gradually lost weight, developed a progressive anemia, and had cutaneous petechiae. On May 7, 1952 he had an embolus to the left leg and on May 12 he was readmitted to the hospital.

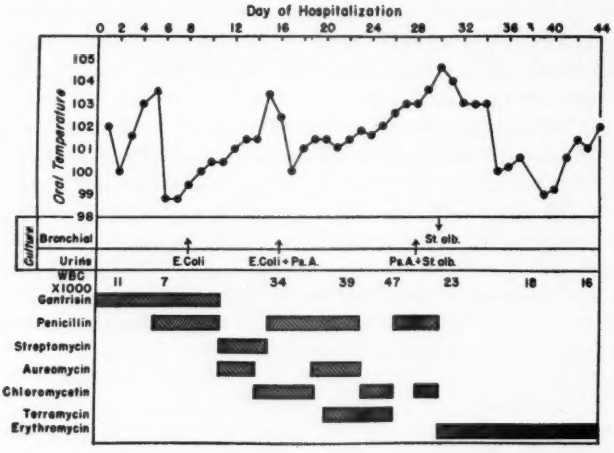

FIG. 1. Resistant staphylococcal purulent bronchitis developing during antibiotic therapy in patient with respiratory paralysis.

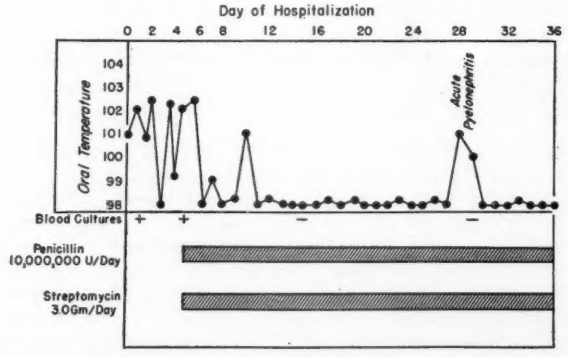

FIG. 2. Enterococcal endocarditis developing following cystectomy for carcinoma.

On examination at this time there was no evidence of recurrence of the malignancy, but he appeared chronically ill. There were rales in both lung bases with enlargement of both the liver and spleen. The left cardiac border was in the midaxillary line and there was a blowing apical systolic murmur. The posterior tibial and dorsalis pedis pulses were diminished on the left. Petechiae were seen on the extremities. A microaerophilic streptococcus was isolated from the blood which was identified as Streptococcus faecalis. In vitro sensitivity tests revealed that this organism was resistant to all antibiotics except to a combi-

nation of penicillin and streptomycin. He was subsequently given 10,000,000 units of penicillin and 3 grams of streptomycin daily by continuous intravenous drip. His temperature promptly returned to normal, but the antibiotic therapy was continued for eight weeks. He has subsequently gained weight and has been well except for three episodes of acute pyelonephritis.

Case 3. A 43 year old farmer was first admitted to the hospital on July 30, 1951, complaining of weakness and dizziness. He was found to have a severe anemia and the diagnosis of myelofibrosis with myeloid metaplasia was ultimately established. From the time of the first admission and the last admission on Aug. 14, 1952 it was necessary to admit the patient to the hospital 16 times for blood replacement and the treatment of frequent respiratory tract infection. During this time the number of polymorphonuclear leucocytes decreased

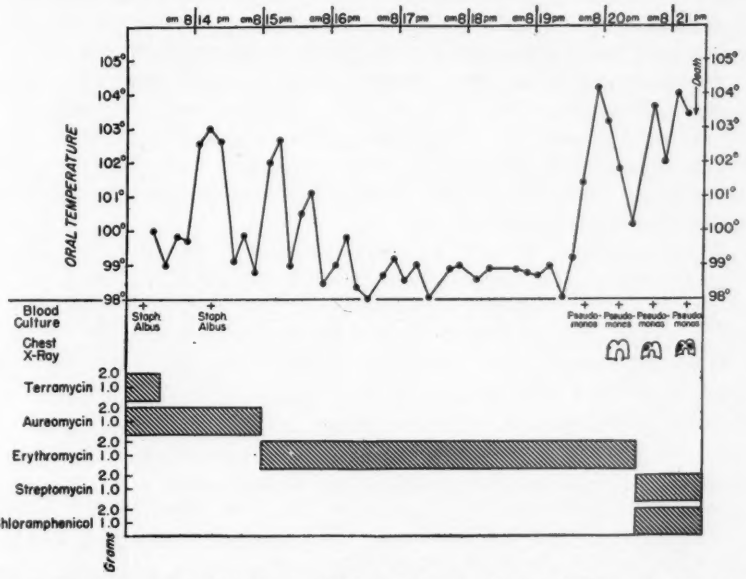

FIG. 3. Pseudomonas septicemia developing during erythromycin therapy of a staphylococcal septicemia in a patient with myelofibrosis.

to less than 5 per cent of the total leucocytes. The infections required treatment with penicillin, aureomycin, terramycin, and chloromycetin at one time or another.

Following a blood transfusion during the next to the last admission on July 26 he developed chills and fever. The chills subsided but he continued to run a low grade fever notwithstanding terramycin therapy until his last admission. Repeated blood cultures were all positive for Staphylococcus albus and this organism was found to be resistant in vitro to all the usual antibiotics, but sensitive to erythromycin. He was consequently readmitted to the hospital and given 2 grams of erythromycin daily with a prompt drop in his temperature and general improvement. On the fifth day of erythromycin therapy, however, he developed a shaking chill, high fever, and acute right chest pain. A few hours later roentgenologic examination of the chest revealed an area of density in the right upper lobe laterally. The following day the chills and fever persisted and the pulmonary disease progressed very rapidly. His sputum contained streaks of blood and was very tenacious. It was the clinical impression that the patient had developed a superimposed septicemia and pneumo-

nia due to a gram negative bacillus which, in view of the sputum, was most likely Klebsiella pneumonia. He was consequently given streptomycin intramuscularly and chloramphenicol intravenously. The pneumonia progressed very rapidly and the patient died a few hours later. After death the cultures of the blood and sputum taken during the last 48 hours of life revealed a pure strain of Pseudomonas aeruginosa.

SUMMARY

1. Some of the less obvious influences of antibiotics on the production and recognition of infections are presented with illustrative case histories.

2. An essential part of the history of any patient with an infection is an exact account of previous antibiotic therapy. This information may aid in making the clinical diagnosis, including the causative organism and its sensitivity, so that the initial therapy prior to final laboratory diagnosis may be as effective as possible.

3. Serious blood stream and metastatic infections may complicate surgical procedures. These should be anticipated and attempts to prevent them may be made by appropriate prophylactic preoperative and postoperative antibiotic coverage. The need for prophylactic coverage is particularly important during surgery in an infected field for the prevention of such serious complications as subacute bacterial endocarditis.

4. The alterations of the normal flora of the body by antibiotic therapy may lead to the loss of some normal inhibitory influences and allow one infection to develop while another is being suppressed. The development of these superimposed infections are most likely to occur if the host's resistance is decreased by a loss of general immunity or local defense and should be suspected if symptoms or signs of an infection occur during antibiotic therapy after an initial therapeutic response.

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HEXAMETHONIUM ILEUS

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The pharmacologic investigations of Paton and Zaimis[16] revealed the quaternary ammonium compounds hexamethonium (C-6), pentamethonium (C-5) and tetramethonium (C-4) to be powerful autonomic ganglion blocking agents. Because of this property, these agents are being employed in the therapy of essential hypertension.

The methonium compounds interrupt the transmission of impulses across autonomic ganglia by preventing the action of acetylcholine on the ganglion cells. Other related quaternary ammonium compounds such as tetraethlyammonium produce autonomic ganglion blockade but lack the freedom from side effects of the methonium compounds, particularly hexamethonium.[15]

The interruption of both sympathetic and parasympathetic outflows by hexamethonium produces not only a reduction in blood pressure but certain undesirable effects as well.[14, 17] Dryness of the mouth, blurring of vision, orthostatic hypotension and constipation commonly occur, and urinary retention may develop. If the dose is increased gradually, however, these undesirable effects are not troublesome and can be controlled with symptomatic therapy. When constipation fails to respond to the administration of laxatives, a parasympathomimetic agent such as urecoline is indicated. Occasionally severe paralytic ileus occurs with marked abdominal distention, absence of peristaltic sounds on auscultation and roentgenographic evidence of small and large bowel distention. This syndrome is well recognized as a complication of hexamethonium therapy and can be managed conservatively if the drug is discontinued and a parasympathomimetic agent is administered. If abdominal pain is associated with the intestinal distention, however, then it becomes necessary to differentiate between the symptoms resulting from hexamethonium administration and those of an acute condition requiring surgical therapy. In the report of Bourne and Hosford[3] a patient receiving hexamethonium developed acute abdominal symptoms for which operation was performed. The entire small intestine was found to be distended, red and endematous, and filled with fluid, and no obstructing lesion was discernible. Mackey and Shaw[13] reported a death which they ascribe to *paralytic ileus* during treatment with hexamethonium compound. At necropsy the small intestine, particularly the jejunum, was grossly dilated with much congestion and edema, and a considerable amount of fluid filled the lumen. No distention nor abnormality was noted in the colon. The jejunum and ileum showed marked necrosis of the mucosa which was thought to be consistent with a pressure necrosis due to accumulation of fluid and gas in the intestines. Recently in consultation we have seen 2 patients on the Medical Service who developed ab-

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dominal symptoms of an acute nature while receiving hexamethonium and presented difficult problems in diagnosis. Since it is not generally recognized that symptoms resulting from hexamethonium administration can closely simulate symptoms resulting from some abdominal disease requiring surgical therapy, these 2 cases are reported.

CASE REPORTS

Case 1. C. H., a 26 year old Latin American man, was admitted to the hospital on Feb. 26, 1952 with a history of hypertension having been discovered in 1946 during a routine physical examination. Since that time he had had increasingly severe headaches. For two

FIG. 1. Case 1. This scout roentgenogram of the abdomen shows moderate distention of the small and large intestine.

years albuminuria and ankle edema had been present intermittently, and for one month he had noticed progressive dimness of vision in the right eye. The blood pressure on admission was 190/130. The retinal arterioles were tortuous and moderately narrowed. On the right there were many old white exudates but no hemorrhages. There was moderate left ventricular enlargement. No other abnormalities were noted on physical examination.

Laboratory data were as follows: Erythrocytes 3,500,000 per cu. mm., leukocytes 6,700 per cu. mm., with a normal differential count, hemoglobin 11.2 grams per 100 cc., urine specific gravity 1,005, albuminuria 4 plus; microscopic examination of the urine revealed 50 to 75 erythrocytes and 5 to 6 leukocytes per high power field. The urine concentration test revealed specific gravity of 1008, 1011 and 1008. The blood urea nitrogen (BUN) was 38 on

admission and subsequently rose to 45, 56 and terminally to 168 mg. per cent. The admission diagnosis was chronic glomerulonephritis and pyelonephritis.

On April 21, 1952 the headaches became more severe, dimness of vision in the right eye increased, and there was blurring of the right optic disc and evidence of recent retinal exudates. Two days later the patient had several clonic convulsions and a diagnosis of diffuse hypertensive encephalopathy was made. Hexamethonium therapy was instituted on April 25. The patient was given a 10 mg. test dose intramuscularly without ill effect. That dose was repeated in 30 minutes, and a significant lowering of the blood pressure occurred. For 48 hours hexamethonium was administered intramuscularly in doses of 20 mg. every two to

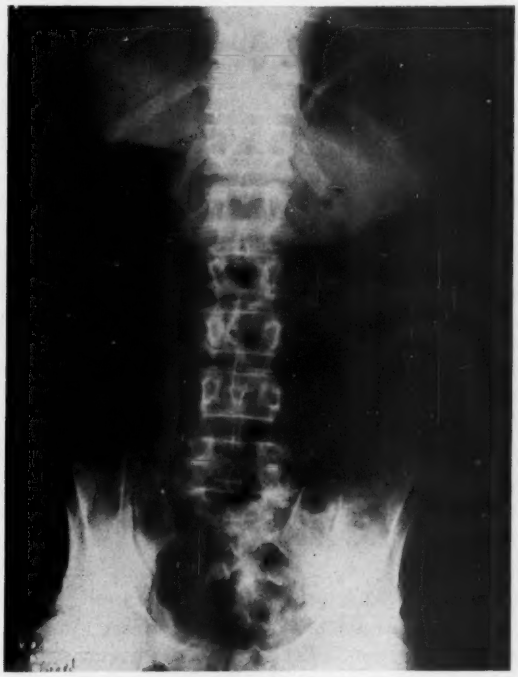

FIG. 2. Case 2. This scout roentgenogram of the abdomen shows marked distention of the small intestine and a moderate amount of air in the colon.

four hours. On this regimen the blood pressure declined somewhat and the convulsive symptoms subsided. On April 27, oral administration of hexamethonium was begun in a dose of 250 mg. every six hours. On April 29, the patient experienced sudden severe lower abdominal pain. A surgical consultant examined the patient and noted generalized abdominal tenderness with rebound tenderness but no appreciable muscle guarding. Peristalsis was hyperactive with high-pitched sounds. The patient was observed closely by personnel of the medical and surgical services for the next 48 hours. During that time his abdominal symptoms increased in severity. The abdominal tenderness became localized to the right mid abdomen, and muscle spasm in the right lower quadrant developed. A roentgenogram of the abdomen revealed large and small bowel distention (fig. 1). A tentative diagnosis of acute appendicitis was made, and although the patient's general condition was poor, it was the consensus that operative intervention was indicated. Operation was performed under

general anesthesia. The colon was greatly distended with air. The small intestine was markedly distended in its proximal portion and completely collapsed distally, although no mechanical obstruction was found. The appendix was normal, as were other abdominal organs. In view of these findings nothing further was done, and the abdomen was closed. Postoperatively, copious bleeding from the incision occurred. The patient became comatose, began to bleed from the gastrointestinal tract as evidenced by melena and hematemesis, and died on May 20, 1952, 18 days after operation. Autopsy was not performed.

Case 2. J. M., a 60 year old Negro man, was admitted to the hospital on July 19, 1952 with a history of hypertensive cardiovascular disease for at least four years and with chronic cardiac decompensation for one year. Physical examination revealed a blood pressure of 225/130 with a pulse of 120 per minute. There were moist rales at both lung bases, and the heart was enlarged to the left. Optic discs were normal, but the retinal arterioles were markedly narrowed. No hemorrhages nor exudates were present. There was pitting edema of the ankles and lower legs. The electrocardiogram was reported as "indicative of left ventricular strain." Blood count and urinalysis revealed no abnormalities. The BUN on successive determinations was 30, 36, 35, 43, and 45 mg. per cent.

The patient's cardiac status improved on treatment with digitalis and mercurial diuretics. On August 14, treatment with hexamethonium was begun. The drug was given orally with an initial dose of 250 mg. every six hours. By the end of the first week this had been increased to 1250 mg. every six hours, and the dose was maintained between 1250 and 2000 mg. every six hours until Octoter 5. During this period he had several episodes of postural hypertension and syncope, however a significant reduction of diastolic blood pressure was achieved. Also during this time he had moderate constipation which was controlled with laxatives and urecoline. On Oct. 5, 1952 he was seen by a surgical consultant because of severe colicky abdominal pain, obstipation of 12 hours' duration, vomiting and abdominal distention. A roentgenogram of the abdomen revealed several loops of dilated small bowel as well as some gas in the colon (fig. 2). There was minimal abdominal tenderness. His temperature and pulse were normal. A diagnosis of hexamethonium ileus was made. The drug was discontinued, an intestinal tube was passed and enemas were given. Within 12 hours the symptoms had begun to subside, and after passing a large stool the patient became asymptomatic. Subsequently he has been treated with other antipressor drugs rather than hexamethonium.

DISCUSSION

The complex activity of the intestinal tract is not well understood today, although many of the classic studies of Bayliss and Starling[1, 2] and of Cannon[6] were made more than 50 years ago. Under normal circumstances, intestinal activity appears to be dependent upon a delicate balance between the parasympathetic and sympathetic components of the autonomic nervous system. With the exception of the sphincters, motor stimulation of the intestinal tract is a function of the parasympathetic outflow, while the sympathetic component is inhibitory. Preganglionic fibers of the sympathetic nerves to the intestines terminate in the celiac and mesenteric plexuses and parasympathetic fibers in the intramural plexuses of Auerbach and Meissner. In the experimental animal the small intestine has been found to remain quite active after combined vagotomy and splanchnicectomy. Pendular and segmental contractions continue and the peristaltic reflex can still be elicited. If the vagus alone is cut, a profound inhibition of the intestines develops which is unrelieved until the splanchnic fibers are cut also. Following combined section of the splanchnic and vagal fibers, stimulation of the

peripheral end of the cut splanchnic nerve produces complete inhibition, whereas prolonged stimulation of the peripheral end of the cut vagus is followed by increased activity of the small intestine. Pendular and segmental movements are a product of the inherent properties of smooth muscle and are unaffected by either extrinsic or intrinsic innervation. Peristaltic movements, although augmented by parasympathetic stimulation, can be continued after section of the extrinsic nerves by reflexes originating in the intrinsic plexuses of Auerbach and Meissner.

Kay and Smith[10] found that the administration of hexamethonium resulted in a diminution of gastric secretion and motility, but the effects of this agent on the human intestinal tract have not been investigated. The effects of tetraethylammonium on the small intestine have been studied, however, and since this drug produces a blockade of autonomic ganglia similar to that of hexamethonium it is probable that the intestinal effects are similar also. In these studies the multiple, intraluminal balloon technic[7] and roentgenographic examination with barium[9, 11] were employed. It was found that immediately upon administration of tetraethylammonium intravenously the tone and propulsive movements of the small intestine were abolished, although segmental and pendular movements continued. No appreciable change in the haustral pattern of the colon was noted, but changes in motility were not determined because of the normally slow progress of the barium meal in the large intestine. Distention of the small intestine with a balloon produced pain, indicating that the visceral afferent fibers were unaffected by the ganglionic blocking agent. That the peristaltic reflex is abolished by tetraethylammonium and not by section of the vagal and splanchnic nerves can be explained by the fact that tetraethylammonium probably blocks vagal impulses at the intramural plexuses, thereby inhibiting both extrinsic and intrinsic nerve pathways.

In view of these observations, paralytic ileus during hexamethonium therapy is a logical development. The cause of the abdominal pain, however, is not so apparent. Two mechanisms are suggested. It is probable that in therapeutic doses hexamethonium does not block autonomic impulses to all levels of the intestines to the same degree. In some segments, tone and peristaltic reflex are completely abolished, in others only slightly diminished, and in others unchanged, while visceral afferent (pain) fibers are unaffected. A paralyzed segment of intestine may present a barrier to the passage of intestinal contents. If this paralyzed segment is adjacent and distal to one in which tone and propulsive movements are normal, hyperperistalsis and intestinal colic ensue, and the symptom complex of acute intestinal obstruction is complete. When intestinal paralysis is more generalized and peristalsis is completely abolished, pain may result from the severe intestinal distention. This clinical picture may mimic closely acute appendicitis or some other abdominal condition of an inflammatory nature which requires operation.

Hexamethonium is becoming widely employed in the treatment of hypertension, and it is not unlikely that paralytic ileus and other symptoms simulating acute abdominal emergencies will be encountered with greater frequency. In view

of the promptness with which these symptoms respond to conservative measures, physicians should be aware of this problem in order to avoid serious errors in diagnosis and therapy.

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TUBERCULOSIS AND CANCER OF THE COLON

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Cancer and tuberculosis have been found side by side in almost every organ of the body. The most common sites include lung, skin and larynx.[9] However, the number of cases which have been reported in these locations is not large, and in other sites the coexistence of the two diseases is rare, despite the fact that both conditions are responsible for a large number of deaths yearly. Rokitansky[7] recognized this fact as early as 1854, and he advanced the theory that the two diseases were antagonistic. This view gained in popularity with the accumulation of statistical data which emphasized the fact that not only was it unusual for cancer and tuberculosis to occur in the same organ, but indeed, it was rare for anyone with tuberculosis to have cancer in any part of the body. Lubarsch[4], in 1888, studied 6,536 necropsy records and found that carcinoma was twice as common in persons without tuberculosis as it is in those with this disease. His study also revealed that patients with any type of cancer were less likely to have tuberculosis than patients without cancer. Pearl[5], also studying necropsy cases, made similar observations. He found that the simultaneous occurrence of the two diseases was even less common when only very active cases of tuberculosis were considered. In such a group he found that the incidence of associated cancer was 1.2 per cent whereas cancer occurred in 9.3 per cent of a non-tuberculous control group. He believed that the antagonism was so strong that he advocated the use of tuberculin for the treatment of cancer.

Notwithstanding this evidence there were others who did not believe that cancer and tuberculosis were antagonistic. The most important statistical study to prove this point was made by Carlson and Bell[1], who studied 11,195 necropsy records. Their findings were similar to those of others in so far as the coexistence of the two diseases was concerned, but they found that when a group of patients with cardiac diseases was studied the incidence of associated carcinoma was even less than that observed in tuberculous patients. In addition, the incidence of tuberculosis in this group was less than in the group with carcinoma. They concluded that tuberculosis and carcinoma were not antagonistic, and that the infrequency with which they were associated was simply a reflection of the fact that a single individual rarely has more than one major disease. Cooper[2] made an extensive review of the literature in 1932 and collected several hundred cases in which cancer and tuberculosis occurred simultaneously in various organs. He concurred with Carlson and Bell that the two diseases were not antagonistic.

At the present time there is nothing to suggest that the conclusions of Carlson and Bell and of Cooper are erroneous, but the coexistence of these two diseases in the same organ remains a rare and interesting finding.

Although the large bowel is a common site for the occurrence of tuberculosis

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and of cancer in individual patients, Randall and Spalding[6] when they reviewed the literature in 1946 were able to collect a total of only 27 cases in which the two lesions occurred simultaneously in this location. Of these, there were 18 in the cecum, 5 in the sigmoid and 4 in the rectum. They added 1 case in which the lesions were found in the splenic flexure. We wish to report 2 additional cases.

Case 1. A 60 year old white man was admitted to the hospital on May 29, 1952 with complaints of fatigue, weight loss, and a dry cough. These symptoms began 18 months prior to admission and progressed in severity during that time. At the time of admission there had been a weight loss of 50 pounds. Weakness was so marked that the patient was almost unable to walk. There had been occasional episodes of fever with night sweats. His cough was productive of one cupful of thick green sputum daily, with occasional episodes of blood streaking. Six months prior to admission a diagnosis of tuberculosis had been made in another clinic on the basis of roentgenogram and sputum examinations. Sanatorium care had been advised, but the patient had refused.

Review of systems revealed that this patient had occasional episodes of epigastric burning pain and mild constipation. Physical examination revealed an emaciated, elderly, white man who appeared acutely and chronically ill. There was slight dyspnea at rest with no cyanosis. He had a cough productive of thick green sputum. The trachea was markedly shifted to the left. Examination of the chest disclosed a slight increase in anterior-posterior diameter. Excursion was limited on the left. Fremitus was diminished over the region of the left upper lobe and the percussion note was flat. Breath sounds were distant over the entire chest, but more so over the region of the left upper lobe. Occasional post-tussis rales were noted in the right interscapular area. Rectal examination revealed a questionable mass above the prostate.

The laboratory examinations included a normal white cell count and differential. Hemoglobin was 12.7 Gm. per 100 cc. with a hematocrit of 42 per cent. Urine examination was negative. Roentgenogram showed infiltration in both upper lung fields with bilateral cavitation. The roentgenologic appearance was that of chronic tuberculosis. Smears and cultures of the sputum were positive for tubercle bacilli.

A proctoscopic examination disclosed a fungating, ulcerating, friable mass on the anterolateral rectal wall, about 8 to 10 cm. above the dentate line. A biopsy specimen of this lesion was reported as "columnar cell carcinoma."

On June 13, 1952 an abdomino-perineal resection was performed for an obstructing carcinoma of the rectum located just beneath the peritoneal reflection. The tumor was free and did not appear to invade the bladder or seminal vesicles. The liver was normal to palpation. There were a few slightly enlarged nodes in the mesocolon, but grossly they did not appear to be involved by the carcinomatous process.

One specimen, 20 cm. long, sent to the Pathology Department for examination consisted of a segment of rectum including the anus with attached adipose tissue and muscle. No enlarged lymph nodes could be found. At one end of this specimen there was a firm mass, 8 by 6.5 by 6.0 cm. On longitudinally cut surfaces, this mass was 9 cm. from the anus and consisted of hard, gray white tissue with small areas of necrosis, that had obliterated the lumen entirely at the proximal and distal ends, leaving a small residual central lumen.

The second specimen was a portion of colon 34 cm. long with attached mesentery. On opening it, the lumen was found to be filled with feces. The wall was 0.3 cm. thick and 14 cm. in circumference. Four cm. from one end there was a pedunculated polyp, 1.5 by 0.7 cm., having a narrow stalk. The mucosal surface otherwise was normal.

Microscopically, tall columnar neoplastic cells with large vesicular or deeply stained nuclei, in places heaped up into several rows, formed irregular acinar tubular structures and replaced the mucosa and submucosa. Nearby there were extensive areas of caseation with palisading of epithelioid cells and many giant cells of the Langhans type. This was contiguous with neoplastic tissue that extended almost through the entire thickness of the

muscular coat. A diagnosis of columnar cell carcinoma of the rectum with tuberculous proctitis was made.

In the pedunculated polyp of the colon, the surface was covered by columnar epithelium that dipped down to form crypts, lined by goblet cells. The fundi of the crypts extended to the muscularis mucosa. Part of the stalk was covered by similar columnar cells, that stopped at the muscularis mucosa. A diagnosis of polyp of the sigmoid colon was made.

The postoperative course was uneventful, and the perineal wound healed without difficulty. During his convalescence this patient also developed a basal cell carcinoma of the

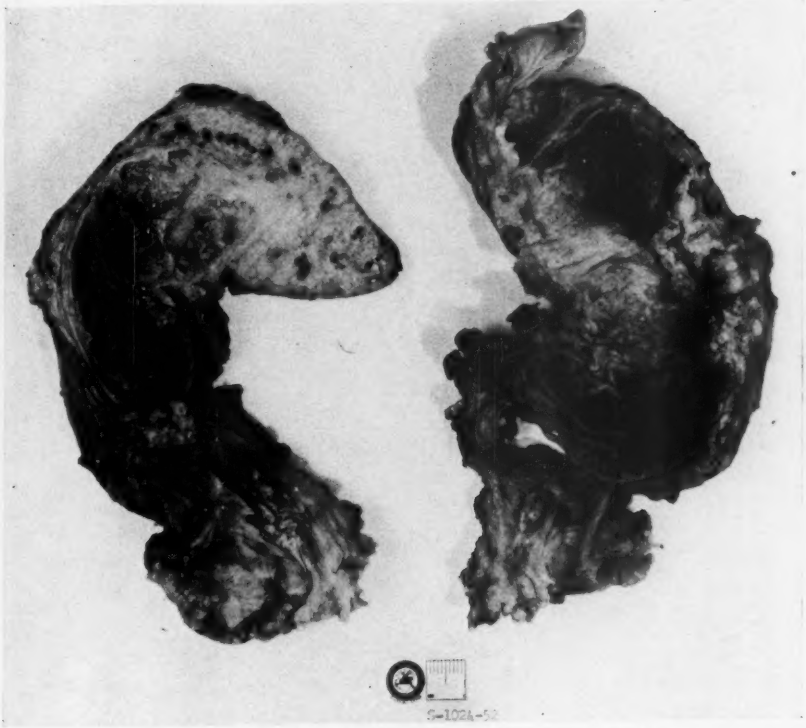

FIG. 1. Case 1. The gross appearance of the resected lesion

face which was adequately treated by radiotherapy. At the present time the patient presents no evidence of any intra-abdominal disease. Roentgenologic examination of the lungs reveals some decrease in the size of the cavity in the left upper lung field. The appearance of the infiltration in both lung fields is approximately the same.

Case 2 A 53 year old white man was first admitted to this hospital in November 1950 with a proved diagnosis of pulmonary tuberculosis. He remained in the hospital until March 1952, at which time his disease was arrested. He returned on May 26, for a follow-up examination. At that time he stated that he had had no fever, cough or sputum; however, for four or five days prior to admission he had had frequent loose stools following a period of excessive alcoholic intake.

Physical examination revealed a generalized flush of the face and a generalized intention

tremor. He was admitted to the hospital with diagnoses of acute alcoholism with *withdrawal reaction* and inactive tuberculosis.

On May 29, the patient had a chill and an elevation of temperature to 102.8 F. His only subjective symptom at that time was passage of gas per urethra. On examination the urine was found to be loaded with white cells and a test for blood was positive. Cultures of the blood and urine were positive for Endamoeba coli. This organism was found to be sensitive to chloromycetin and resistant to penicillin and streptomycin; therefore, treatment with chloromycetin was instituted.

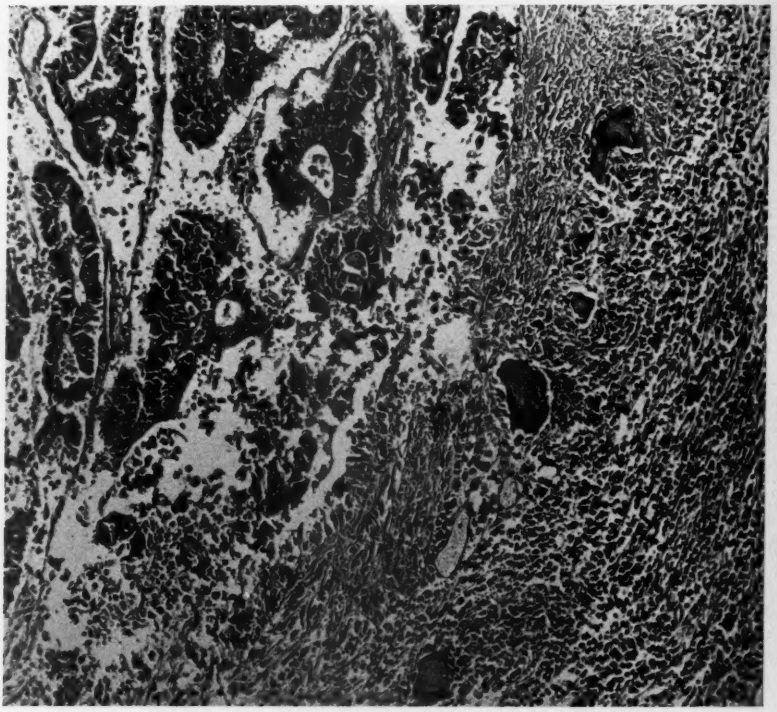

FIG. 2 Case 1. Carcinoma adjacent to tuberculous focus containing epithelioid cells, inflammatory cells, and giant cells of the Langhans type (× 100).

A diagnosis of sigmoidovesical fistula was entertained, but repeated cystoscopic examinations failed to reveal any opening into the bladder, and a retrograde pyelogram did not demonstrate a ureteral or nephric fistula. Sigmoidoscopy was attempted on three occasions. No mucosal pathology could be seen, but the proctoscope could not be passed beyond 18 cm. because of narrowing and angulation of the bowel. A barium enema revealed a filling defect in the sigmoid with marked spasm in this area.

On July 16, the diagnosis of sigmoidovesical fistula was confirmed when the patient passed a large amount of definitely fecal material per urethra. A surgical consultation was requested, and operation was advised with a preoperative diagnosis of sigmoidovesical fistula, probably due to diverticulitis or to carcinoma.

At operation on July 29, an inflammatory mass in the sigmoid with a sigmoidovesical

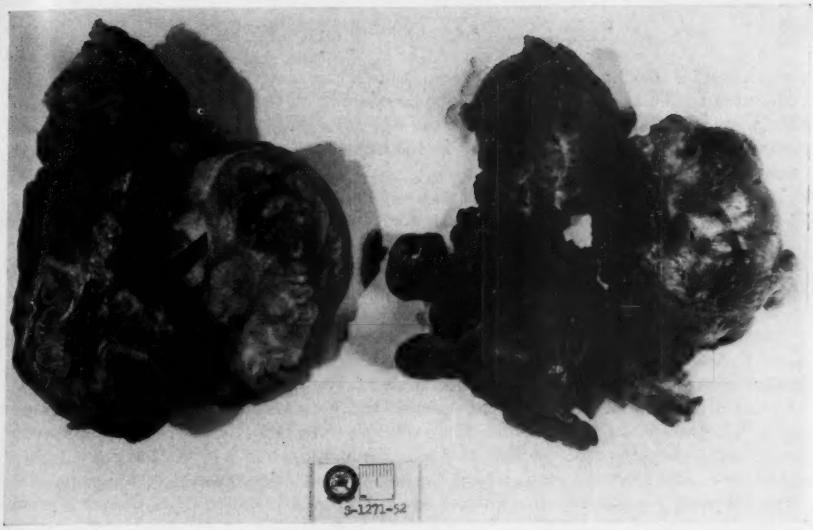

FIG. 3. Case 2. The gross appearance of the resected lesion

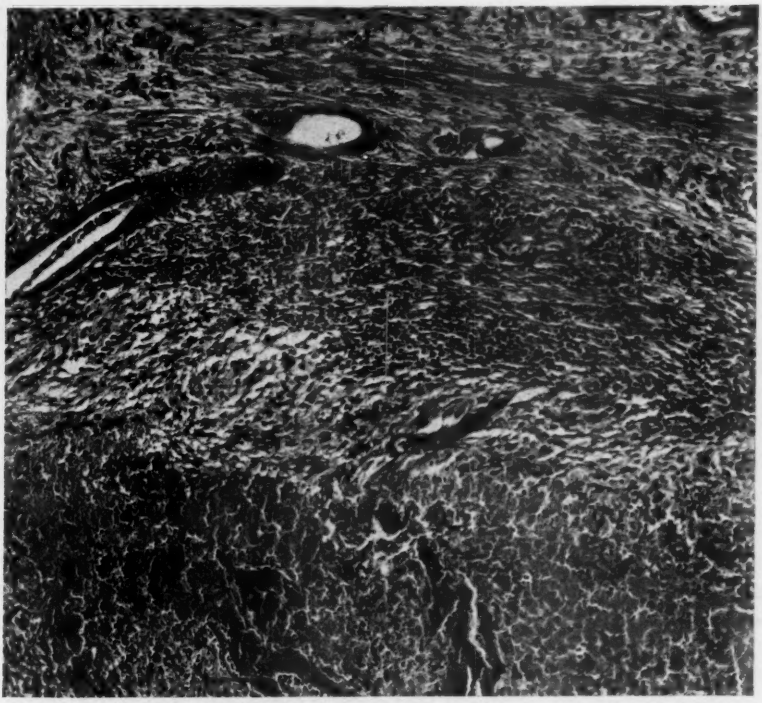

FIG. 4. Case 2. Carcinoma adjacent to area of caseation surrounded by epithelioid zone, inflammatory cells, and a single giant cell (× 100).

fistula entering the dome of the bladder was found. The mesentery of the bowel was quite inflamed and edematous. Examination of the remainder of the abdominal cavity was completely negative. A primary resection of the sigmoid with an end to end anastomosis and closure of the opening of the fistula into the bladder was performed. A transverse loop colostomy was established also.

The specimen submitted for pathological examination consisted of a segment of colon, 20 cm. in length, that was folded upon itself with the adjacent surfaces adhered by fibrin and somewhat firmer, partially necrotic tissue. The central portion was firm to palpation over an area 10 by 6 by 6 cm. On longitudinally cut surfaces the lumen was almost obliterated by firm, gray white, apparently neoplastic tissue that was interspersed by yellow necrotic areas. There was 5 cm. of normal appearing mucous membrane at either end.

Microscopically, the surface was partially covered with tall neoplastic cells that dipped down to line irregular acinar-tubular structures. The cells contained oval or elongated, vesicular or deeply stained nuclei and abundant cytoplasm. Cells in various stages of atypical division were numerous. This neoplastic tissue extended into the outer muscle coats. Nearby were large fields of fibrous connective tissue with focal areas of lymphocytes, necrosis and discrete tubercles of epithelioid cells and giant cells of the Langhans type. A diagnosis of columnar cell carcinoma of the colon with tuberculous colitis was made. Two days following operation a urine culture which had been taken on June 17, was reported positive for tubercle bacilli.

The postoperative course was uneventful, and on Sept. 19, 1952 the colostomy was closed. Since this operation the patient has had normal bowel movements, and urination has been normal since the first procedure. Repeated urine examinations have been negative. There is no evidence of residual disease in the abdomen at this time, but unfortunately this patient again has sputum positive for tubercle bacilli.

COMMENT

During the past three years a total of 89 malignant lesions of the large bowel have been treated at this hospital. It is interesting that in this short time we should see 2 cases with associated tuberculosis, and particularly so since both cases had involvement of the left side of the colon.

Case 2 is the only case reported in which there was an associated sigmoidovesical fistula. Spontaneous sigmoidovesical fistulas due to tuberculosis are quite rare, and cancer of the sigmoid does not usually result in fistulous formation until the process is far advanced. At the time of operation it was thought that the fistula was secondary to the inflammatory process as there was no gross neoplasm evident, but since the microscopic sections showed both lesions in the region of the fistula, it is not possible to be absolutely certain which disease resulted in the development of this complication.

When one finds two lesions associated so closely, as they were in these 2 cases, it is always interesting to speculate whether or not one disease process initiated the second. Some observers have postulated that a chronic tuberculous lesion was a good site for the development of cancer, while others have believed that a cancer was a good media for the growth of tubercle bacilli.[5] It is plausible that ulceration secondary to malignant disease might provide a portal of entrance for any type of organism. As it is well known that cancers of the colon do become secondarily infected with other organisms which are normally in the gastrointestinal tract, it is not inconceivable that such an area might become infected with the tubercle bacillus. Also it has been noted that tuberculosis of the intestines

occurs most commonly at points of obstruction in the bowel—such as the ileocecal junction.[3] It is possible that an obstructing carcinoma might have a similar effect. Although existing evidence does not seem adequate to prove either point, cases such as the 2 we are reporting seem to lend credence to these concepts.

SUMMARY

A brief review of the literature on the simultaneous occurrence of tuberculosis and carcinoma in the large bowel has been presented. Two additional cases are reported, both of which involved the left colon.

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THE INTRATHORACIC USE OF STREPTOKINASE-STREPTODORNASE

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In 1949 Tillett and Sherry reported the intrathoracic use of the streptococcal concentrates streptokinase-streptodornase (SK-SD) in the therapy of certain sanguineous and purulent intrapleural collections.[12] Subsequently, other reports[1, 2, 7, 8, 14, 15] have appeared describing utilization of these agents in the management of thoracic empyema, hemothorax and certain other pleural exudates.

The properties of streptokinase and streptodornase, (SK-SD) which are derived from broth cultures of certain strains of beta hemolytic streptococci,[3, 9, 10, 11, 13] have been intensively studied. Streptokinase acts as a catalyst, activating a fibrin-lysing system (plasminogen) present in the euglobulin fraction of blood which causes lysis of fibrin and also inhibits conversion of fibrinogen to fibrin. In contrast, SD is not a single entity but consists of progressively acting enzymes which bring about depolymerization of desoxyribonucleoprotein, in the presence of the magnesium ion. The ability of these agents to produce liquefaction of fibrin and hydrolysis of nucleoprotein led to their use in sanguineous intrapleural collections where fibrin is the major substrate, and purulent pleural exudates where nucleoprotein constitutes from 30 per cent to 70 per cent of the solid sediment.

This report describes our experience with the intrathoracic use of SK-SD in the management of 43 patients on a thoracic surgical service. The cases have been divided into three categories:

1. Empyema—16 Cases
2. Hemothorax—18 Cases
3. Miscellaneous—9 Cases

GENERAL PLAN OF MANAGEMENT

In the management of pleural exudates, therapy should be directed toward complete removal of the intrapleural deposit, eradication of infection, if present, and restoration of pulmonary function by re-expansion of the lung. The decision to employ SK-SD alone or in combination with other forms of therapy should be based upon the particular problem presented by each case.

The extent of the intrapleural collection and the location of loculations are determined by fluoroscopy and postero-anterior and lateral roentgenograms. Aspiration with removal of as much fluid as possible is carried out at one or more sites. Multiple locules are aspirated separately. A solution of 200,000 to 400,000 units of SK to 100,000 to 200,000 units of SD in 25 to 50 cc. of physiologic saline is injected intrapleurally at the sites of aspiration. Eighteen to 24 hours later any

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change in the number or location of loculations is determined by fluoroscopy or roentgenograms and aspiration is repeated. If multiple locules persist, the enzymatic solution is again placed within the chest following aspiration. On the other hand, if multiple pockets have been converted into a single deposit and the amount of fluid aspirated indicates relatively complete evacuation of the pleural space, additional enzymatic therapy is deferred. The clinical course and roentgenographic changes thereafter determine whether or not SK-SD therapy should be continued. Frequently, complete roentgenographic clearing does not occur promptly to a degree commensurate with the amount of exudate removed from the chest and the improvement in pulmonary function which has taken place. However, clearing will usually be noted within two to three weeks if SK-SD therapy has been successful.

When the intrapleural deposit is extensive and pulmonary collapse a significant factor, closed thoracostomy may be advantageous. Under local anesthesia a No. 20 to 26 catheter is passed into the chest through a dependent intercostal space and connected to an underwater drainage bottle. The catheter is used as one of the sites of instillation of the enzymatic solutions, then clamped until aspiration is performed. When SK-SD solutions are not being used, the catheter is connected to a suction pump via the drainage bottle and a negative pressure of minus 6 to minus 8 cm. of water applied to assist re-expansion of the lung. Empyema of relatively long standing is less responsive to the action of the streptococcal concentrates because of the thickness of the pleural exudate, and in these cases therapy must be applied persistently.

The intrathoracic use of SK-SD is followed by production of specific antibodies because of the antigenic properties of these agents. If therapy is prolonged, it may be necessary to increase the amounts of SK-SD administered in order to overcome the neutralizing effect of these antienzymes.

Toxic responses are common during the course of enzymatic therapy and will generally coincide with the interval between injection and aspiration of the SK-SD solution. In a majority of cases the reaction is febrile, often associated with general malaise, leukocytosis and the appearance of formed elements in the urine,[5] and can be controlled by administration of antipyretics and prompt (18 to 24 hours) removal from the chest of the liquefied substrates. In none of our patients has the reaction persisted after discontinuance of enzymatic therapy.

ANALYSIS OF CASES

1. Empyema

Until the introduction of the antimicrobial agents thoracic empyema was generally considered to be a surgical problem best treated by thoracostomy. The antimicrobials made possible successful medical management of some cases; yet when loculations developed, the purulent fluid became viscid, or the empyema was of the *putrid* type, surgical drainage was still necessary. The discovery by Tillett and associates of the presence in significant amounts of nucleoprotein in the solid sediments of purulent pleural exudates, and the isolation of streptococcal desoxyribonuclease streptodornase (SD) as a companion substance to strepto-

kinase, (SK) made possible a new approach to this problem. Applied topically, these agents, by fibrinolysis and hydrolysis of nucleoprotein, break up loculations and cause thinning of the purulent fluid and pleural exudate. Liquefaction of the solid elements of the exudate and thinning of the viscous fluid promote phagocytosis by leucocytes and increase the effectiveness of antimicrobial therapy. Eradication of infection, evacuation of the pleural exudate and re-expansion of the lung are thereby often made possible without resort to operative measures.

The 16 patients with empyema treated with SK-SD have been divided for purposes of discussion into four groups, based on the associated thoracic condition:

A. Postpneumonic Empyema
B. Tuberculous Empyema
C. Postpneumonectomy Empyema
D. Other Postoperative Empyemas

A. Postpneumonic Empyema

Not only have the antimicrobial drugs reduced the incidence of bacterial pneumonia and related empyema, but they have also been successfully employed topically in the treatment of this type of empyema. Generally, the appearance of loculations or a highly viscous exudate which resists aspiration will require additional therapeutic measures and it is in this type of case that we have used enzymatic therapy.

Four patients with postpneumonic empyema have been treated with SK-SD (Table 1).

As a result of the extensive antimicrobial therapy that preceded the use of SK-SD the purulent exudate in all cases was sterile. In 3 patients the empyema was multilocular, which rendered needle aspiration ineffectual. In the third patient, an infant, the purulent fluid was so thick as to make aspiration unsatisfactory.

The number of injections (days of therapy) varied from two to seven. Because of a thickened visceral pleura and slow re-expansion of the lung, SK-SD solutions were used on seven different occasions over a period of one month in case 4 whereas in the other 3 patients, response to the enzymes was prompt. In all cases the use of SK-SD solutions made possible the successful evacuation of the empyema cavity via needle aspiration and re-expansion of the lung.

Case 2 is presented to illustrate the methods by which SK-SD is employed in the management of postpneumonic empyema.

W. M., a 55 year old white man, was admitted to the hospital because of cough, fever, pain in the right side of the chest, and progressive weakness for two months. Roentgenograms revealed an opacity throughout the right pulmonary field with multiple fluid levels (fig. 1 a). Aspiration of two locules yielded 300 cc. of serous fluid and approximately 150 cc. of air. A solution of 100,000 units of SK and 60,000 units of SD in 20 cc. of physiologic saline was injected intrapleurally at the sites of thoracentesis. Eight hours later fluoroscopy revealed disappearance of the fluid levels, and aspiration yielded 1,000 cc. of thick, purulent exudate (fig. 1 b). Three days later fluoroscopy disclosed reaccumulation of fluid and 450 cc.

of purulent material was removed with amelioration of symptoms. In view of the large size of the empyema cavity, a no. 24 catheter was inserted, under local anesthesia, through the eighth intercostal space in the posterior axillary line, and minus 8 cm. of pressure applied through an underwater drainage bottle. Six days later re-expansion of the lung was incomplete because of a thick, visceral pleural exudate (fig. 1 c). A solution of SK-SD was placed into the empyema cavity through the intercostal catheter, which was then clamped. Twenty-four hours afterward the catheter was opened, suction applied, and within three

TABLE 1

Results of SK-SD therapy in 16 patients with empyema

Type	Pt. No.	Culture	Duration Days	Loculation	Injections SK-SD Days of therapy	Results		
						Succ.	Part. Succ.	Unsucc.
Post-pneumonic	1	Sterile	20	Yes	3	X		
	2	Sterile	14	Yes	2	X		
	3	Sterile	7	No	2	X		
	4	Sterile	7	Yes	7	X		
Tuberculous	5	A.F.B.	96	No	2			X
	6	A.F.B.	49	Yes	1	X		
	7	A.F.B.	49	Yes	14			X
	8	A.F.B. Staph. aureus	140	Yes	11			X
Post-pneumonectomy	9	H. staph. aureus	20 p.o.	Yes	6	X		
	10	B. proteus	11	Yes	5		X	
	11	E. coli	12	Yes	2		X	
	12	H. staph. aureus	64 p.o.	Yes	8	X		
Other postoperative	13	E. coli	5 p.o.	Yes	1			X
	14	B. pseud.	2 p.o.	Yes	1	X		
	15	B. proteus	8 p.o.	Yes	4	X		
	16	Sterile	10 p.o.	Yes	1	X		

days pulmonary re-expansion was complete. Roentgenograms taken approximately one month after institution of enzymatic therapy showed only slight pleural scarring (fig. 1 d).

Comment: This case dramatically demonstrates the effectiveness of SK-SD in reducing multiple empyemal pockets to a single collection. Only one application of the enzymes was required to permit complete evacuation of the empyema cavity. The intercostal catheter made it possible to maintain an effective negative pressure within the empyema cavity and provided a portal for further enzymatic solutions.

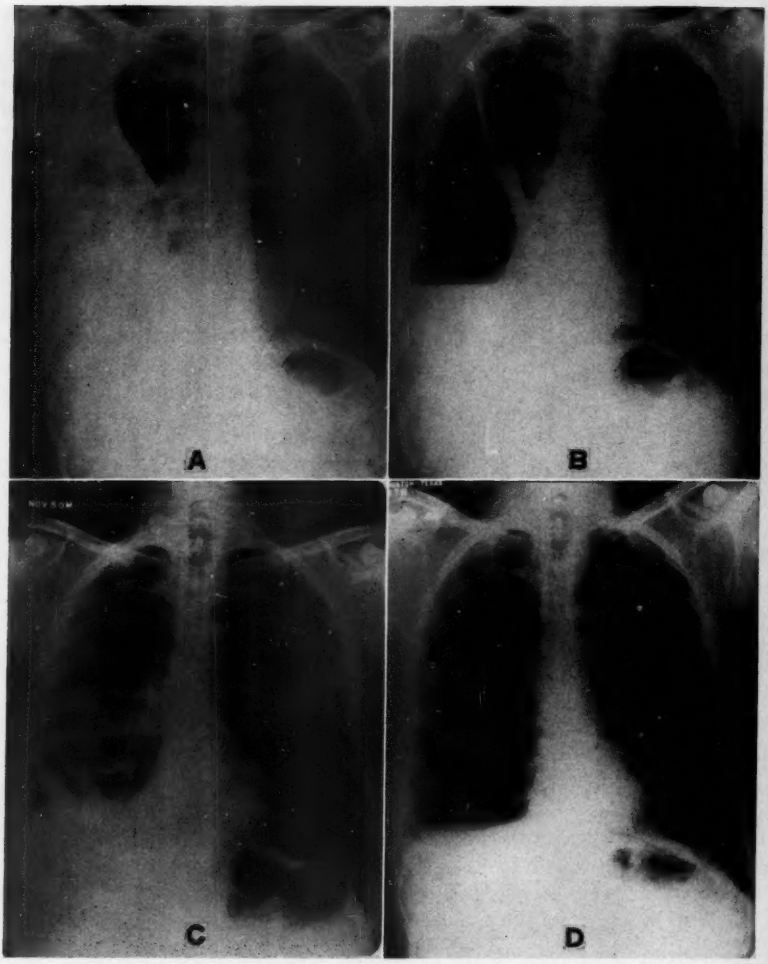

FIG. 1. Case 2. Post-pneumonic empyema—Roentgenograms (a) prior to SK-SD therapy, (b) 18 hours after SK-SD and after removal of 1000 cc. of fluid, (c) after one week of catheter drainage and suction and just prior to second application of SK-SD, and (d) one month after beginning enzymatic therapy.

B. Tuberculous Empyema

It has been observed that the streptococcal concentrates do not affect living cells or organized fibrous tissue, and in view of the frequency with which fibrous tissue elements invade the pleural exudate in chronic empyema one might expect the enzymatic agents to be least effective in pleural infections of long standing. This is especially true when the empyema is tuberculous and follows an effusion which develops during the course of artificial pneumothorax. Under these condi-

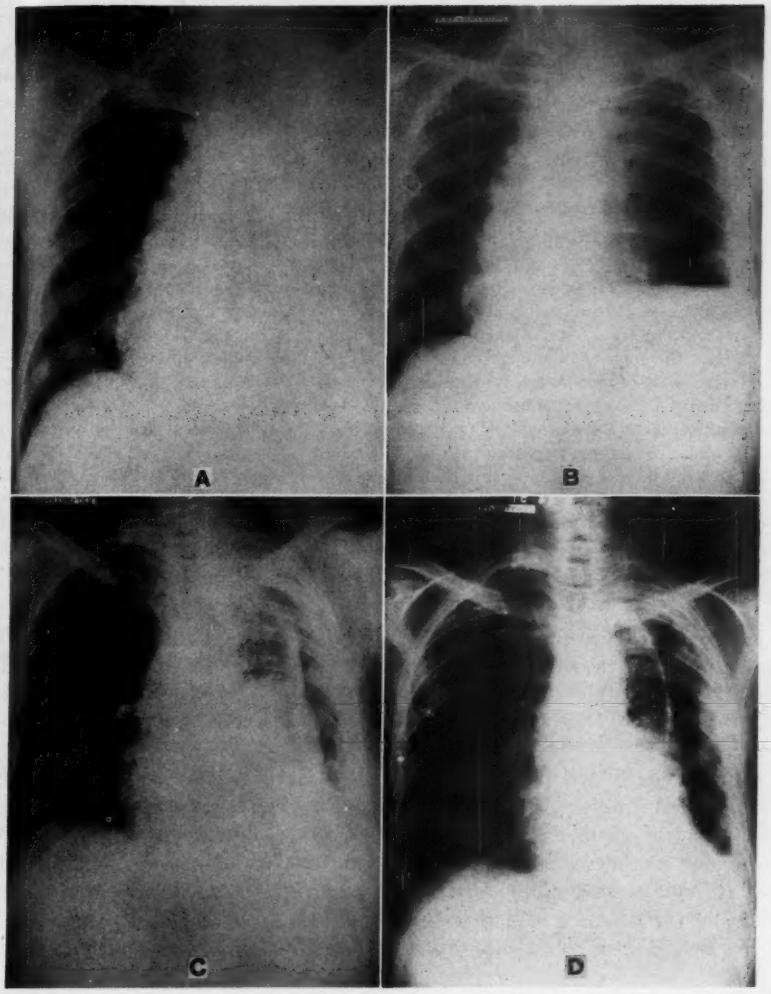

FIG. 2. Case 7. Tuberculous empyema—Roentgenograms (a) on admission showing massive hydrothorax, (b) after aspiration of 2200 cc. of purulent fluid, (c) after thoracentesis following initial use of SK-SD, and (d) after six weeks of SK-SD therapy.

tions the lung is held captive by a fibropurulent rind and generally surgical decortication is required to release the lung. We have found this to be true in our experience with 4 cases of tuberculous empyema (Table 1). In 2 of these, cases 5 and 8, the empyema developed during artificial pneumothorax therapy for pulmonary tuberculosis. In the former, enzymatic therapy was discontinued before being given an adequate trial, but the findings at operation (decortication and right upper lobectomy) of a thick, fibrous rind over the surface of the lung indi-

cated that enzymatic debridement would have been ineffectual had it been continued. In case 8, SK-SD was used first in an attempt to eradicate the empyema and re-expand the lung. When this failed, decortication was performed and although the lung re-expanded, multiple, purulent pockets persisted and vigorous enzymatic therapy was ineffectual in eradicating them. In case 6 the empyema, which was of relatively short duration, was successfully managed with the enzymatic agents.

Since case 7 is representative of the results which can generally be anticipated in chronic tuberculous pleural infection, it will be described in detail:

Case 7. W. T., a Negro man 30 years old, was admitted to the hospital with a history of fever of five weeks duration, night sweats, loss of weight, cough productive of thick yellow sputum, and shortness of breath on exertion. A roentgenogram (fig. 2a) revealed an opacity throughout the entire left hemithorax with a shift of the mediastinum to the right and an infiltrative process in the right apical and subapical areas. A diagnosis was made of pulmonary tuberculosis with massive pleural effusion. Thoracentesis on two occasions yielded a total of 220 cc. of greenish yellow purulent material (fig. 2 b). Nine days after admission a no. 26 rubber catheter was placed into the left hemithorax and a solution of 600,000 units of SK to 300,000 units of SD was instilled in the chest through the catheter. Eighteen hours later aspiration yielded 1000 cc. of purulent fluid from which tubercle bacilli were cultured (fig. 2 c). During the next six weeks the patient had 13 intrapleural applications of SK-SD solution. At the end of this time the lung remained collapsed and a pleural exudate was still visible in the roentgenogram (fig. 2d). At this time enzymatic therapy was discontinued, and surgical decortication was carried out.

Comment: Neither the size of the empyema cavity nor the thickness of the pleural exudate were appreciably altered by vigorous SK-SD therapy in this case.

C. Postpneumonectomy Empyema

Careful closure and pleuralization of the bronchus, and prophylactic use of antimicrobial agents have effectively reduced the incidence of intrapleural infection following pneumonectomy, but this condition still remains one of the most distressing complications of pulmonary resection. Although successful management of this type of empyema by conservative measures has been reported,[6] generally the presence of multiple, infected locules, bronchial fistulas, or both have required open thoracostomy and manual evacuation of the infected coagulum.

The fibrinolytic action of the streptococcal concentrates has been shown to bring about prompt liquefaction of the coagulum permitting evacuation of the infected thoracic space by other than operative means, thus affording another effective approach to this problem. In the absence of an associated bronchial fistula, the enzymatic agents are employed in approximately the same amounts as are used in treating post-pneumonic empyema. An intercostal catheter inserted under local anesthesia at a dependent level is routinely used in these cases to facilitate drainage of the thoracic space. Cultures and antimicrobial sensitivity studies are carried out daily on the aspirated fluid, and the appropriate agent is employed. Persistence of the intrapleural infection may indicate that further

SK-SD therapy is needed to complete debridement of the pleural exudate and allow antibiosis to take place more effectively. Once the cultures have become sterile, and remain so for at least two weeks, the catheter is removed and antibiotic therapy discontinued.

The presence of a bronchial fistula renders unlikely the possibility that enzymatic therapy will be completely successful. Small fistulas may close once the infected coagulum has been removed, although in our experience such a possibility is remote. However, the loculated pleural space can be evacuated without resorting to open thoracostomy, and the problem of the fistula can be attacked later. In the interval between the first injection of the enzymatic agents and drainage of the chest, care must be taken to prevent aspiration of the liquefied coagulum through the open bronchus into the opposite bronchopulmonary tree.

We have employed SK-SD solutions in 4 patients with post-pneumonectomy empyema (Table 1). In cases 10 and 11, the diagnosis was established coincident with the development of bronchial fistulas on the eleventh and twelfth postoperative days, respectively. The intrapleural infection in cases 9 and 12, unassociated with a bronchial leak, did not become apparent until the twentieth and sixty-fourth days, respectively. In all instances multiple loculations were demonstrable roentgenographically. The infecting organism in each case was determined by culture. The simultaneous elimination of both gram-positive and gram-negative organisms by the broad-spectrum agent, aureomycin, probably was responsible for the growth of Bacillus proteus in case 10. This infection was never controlled although polymixin was given both systemically and topically.

The number of injections of SK-SD varied from two to six. In all instances, no more than two injections of SK-SD were required for liquefaction of the infected coagulum. Subsequent injections were employed for debridement of the exudate on the pleural surfaces and eradication of infection.

That the results of SK-SD therapy were completely successful only in the 2 patients, (cases 9 and 12) without bronchial fistulas is to be expected. In these two instances the intrapleural infection was eliminated and the patients have remained well for 26 and 12 months respectively. In cases 10 and 11, the infected pleural space was successfully evacuated but persistence of large bronchial leaks necessitated continued drainage and finally open thoracostomy in case 11. These cases are listed as partially successful only in that evacuation of the coagulum was accomplished by the use of SK-SD.

The case histories of patients 9 and 10 are presented to illustrate utilization of enzymatic therapy in postpneumonectomy empyema with and without bronchial fistula.

Case 9. A. H., a Negro man, 45 years old, had a pneumonectomy for squamous cell carcinoma of the left upper lobe of the lung. Three weeks later dyspnea and low grade fever developed. Culture of the fluid from the left thoracic space yielded hemolytic staphylococcus aureus. An attempt was made to manage the empyema by needle aspiration and topical application of penicillin and streptomycin. Loculations (fig. 3a) appeared, however, and SK-SD therapy was instituted. A no. 18 catheter was inserted through the eighth interspace under local anesthesia and approximately 200 cc. of sanguino-purulent fluid removed. A

solution of 180,000 units of SK and 63,000 units of SD in 20 cc. of physiologic saline was injected into the left pleural cavity through the catheter. Twenty-four hours later the catheter was opened and the cavity drained (fig. 3b). The thoracic space was then irrigated with

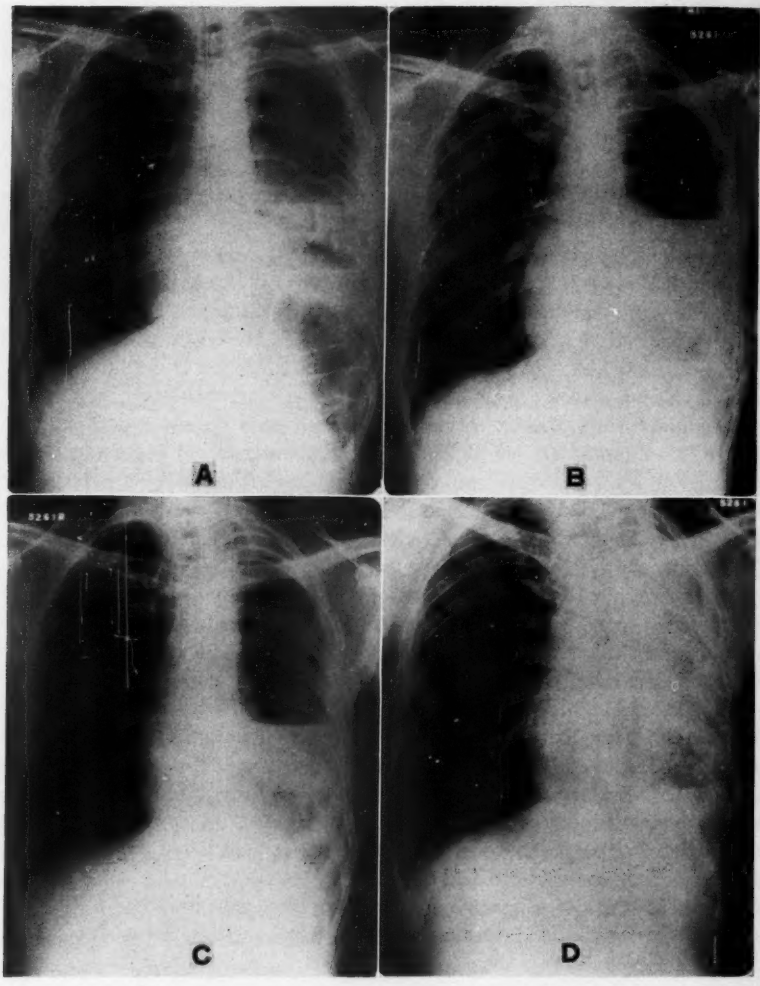

FIG. 3. Case 9. Post-pneumonectomy empyema—Roentgenograms (a) prior to injection of SK-SD, (b) 24 hours later, after drainage of the thoracic space through the intercostal catheter, (c) 44 days after enzymatic therapy began, and (d) eight months following discharge from hospital.

250 cc. of a solution of physiologic saline containing 500 units each of streptomycin and bacitracin. Aspiration of the chest and irrigation were repeated daily and five injections of enzymatic solutions were given over a period of eight days. Sixteen days after SK-SD

therapy was instituted aspiration yielded only 75 cc. of fluid, which was now serous in character, although cultures still yielded positive results. The catheter, which had become occluded, was removed. Aspiration and irrigation were discontinued until the forty-first day

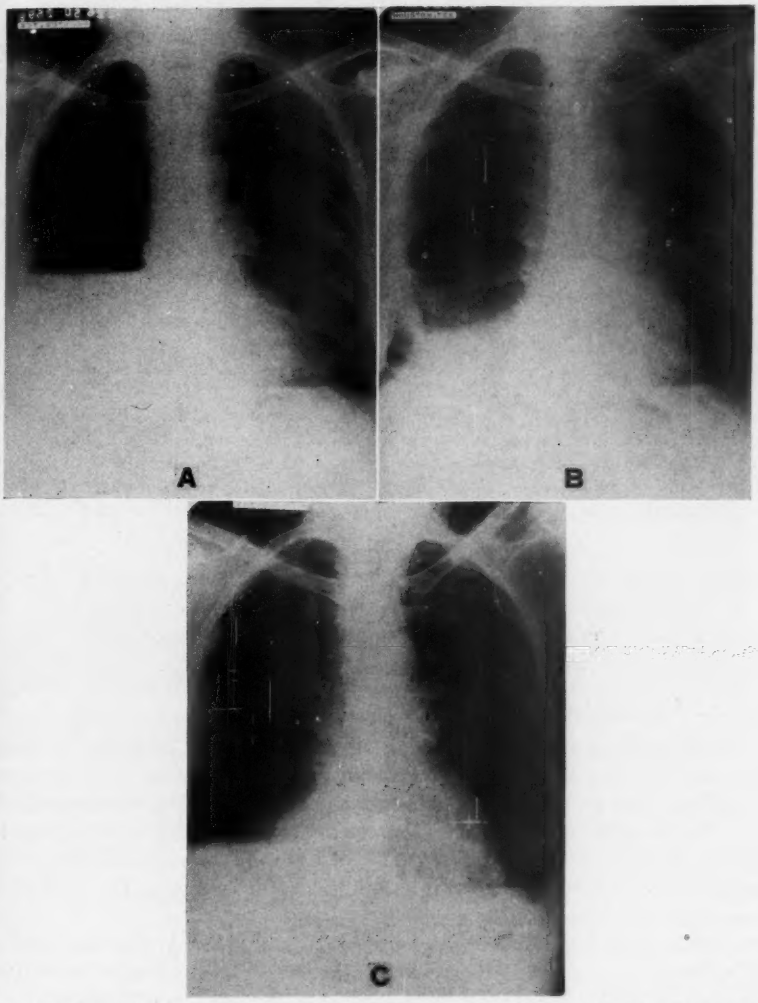

FIG. 4. Case 10. Post-pneumonectomy empyema—Roentgenograms (a) prior to first injection of SK-SD, (b) 18 hours after initial therapy with SK-SD and following removal of 600 cc. of fluid, and (c) after six daily injections of SK-SD.

when aspiration yielded approximately 200 cc. of serous fluid, which proved to be sterile on culture, and antimicrobial therapy was discontinued (fig. 3 c). The patient was discharged subsequently. Roentgenograms three months later revealed organization and obliteration of the thoracic space (fig. 3d).

Comment: This was our initial effort at enzymatic therapy for post-pneumonectomy empyema. Further experience has indicated that larger doses (200,000 to 400,000 units) of SK will bring about more rapid liquefaction of the coagulum and debridement of the pleural exudate. The effectiveness of antimicrobials applied topically is questionable, but the irrigative action of the solution in dislodging the pleural exudate probably warrants its use in some instances.

Case 10. D. R., a white man, had palliative pneumonectomy for carcinoma of the right lung. Because of an abscess distal to the carcinoma the patient received penicillin for approximately two weeks preoperatively, and aureomycin postoperatively. On the eleventh postoperative day he became hypotensive and began expectorating large amounts of thin sanguineous fluid, and a diagnosis of bronchial fistula was made (fig. 4 a). Pneumonitis of the left lung developed, probably as a result of aspiration of pleural fluid through the fistula. A no. 26 catheter was inserted through the ninth intercostal space and approximately 500 cc. of fluid was aspirated. Roentgenograms indicated that a large amount of infected clot remained, and 100,000 units of SK and 600,000 units of SD were injected through the third interspace anteriorly. Eighteen hours later the catheter was opened and 600 cc. of serosanguineous fluid was removed (fig. 4b). During the succeeding six days solutions were injected on four different occasions, one-half through the catheter and one-half via needle through a higher interspace. Daily thoracenteses yielded a total of 800 cc. of serosanguineous fluid, from which Bacillus proteus was obtained on culture. Polymixin to which the organisms were shown to be sensitive was administered intramuscularly and topically by daily irrigation of the infected pleural space with 250 cc. physiologic saline solution containing 25 mg. of polymixin. Although the fibrinous coagulum had been removed (fig. 4 c), the intrapleural infection persisted and the patient died on the thirty-third postoperative day.

Comment: In view of the palliative nature of the pulmonary resection, drainage of the infected pleural space was all that could be reasonably expected. This was accomplished by means of enzymatic therapy and closed thoracostomy; thus the disagreeable after-care of open thoracostomy was avoided.

D. Other Postoperative Empyemas

This group consists of 4 patients in whom intrapleural infections developed following intrathoracic surgical procedures (Table 1). In case 16 a neurogenic mediastinal tumor was removed with subsequent development of a pleural infection. Despite surgical decortication, pulmonary re-expansion was incomplete and multiple purulent pockets persisted. The SK-SD were therefore injected into the largest of the locules, and following aspiration of a large quantity of fluid the lung re-expanded completely.

In the 3 remaining cases in this group, 13, 14 and 15, empyema developed following esophageal resection. This complication is generally managed by establishment of an esophagopleural cutaneous fistula through open thoracostomy, a procedure which has generally proved satisfactory; yet the prolonged drainage from a large, open wound, and the length of time required for pulmonary re-expansion are distinct disadvantages to this form of therapy. The success achieved with the enzymatic agents in the management of other types of empyema prompted us to utilize them in treating intrapleural infections resulting from a leaking

esophageal anastomosis, and since the use of enzymatic therapy in this type of case has not previously been reported, 2 of these cases are presented.

Case 14. R. K., a Negro child two years old, sustained a lye burn of the esophagus at the age of one year. Stricture developed in the middle third of the esophagus and gastrostomy and retrograde dilations were ineffectual. Right thoracostomy was performed. A stricture 2 cm. in length at the level of the aortic arch was excised and end to end esophageal anastomosis accomplished. On the fifth postoperative day a collection of fluid and air in the right apex led to the diagnosis of a leak at the anastomosis (fig. 5 a). Thoracentesis in the second right interspace anteriorly yielded approximately 50 cc. of cloudy, serous fluid from which Bacillas pseudomonas was cultured. A solution of 100,000 units of SK and 48,000 units

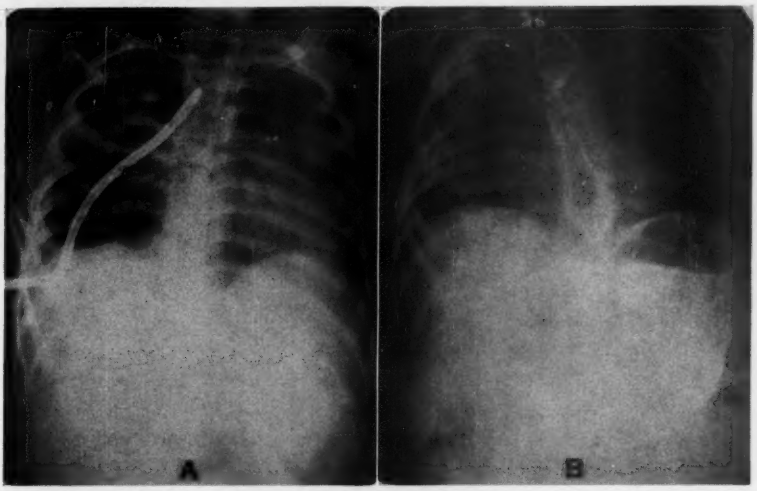

FIG. 5. Case 14. Postesophageal resection empyema—Roentgenograms (a) on fifth postoperative day, showing apical loculations and prior to SK-SD therapy, and (b) two weeks after enzymatic therapy. Barium outlines esophagus and indicates closure of fistula.

of SD dissolved in 10 cc. of physiologic saline was injected at the site of aspiration. Twenty-four hours later roentgenograms revealed a collection of fluid at the right base and considerable diminution in the size of the apical collection. The intercostal catheter, inserted at the time of aspiration, had become occluded and was removed. Under light, general anesthesia a 3 cc. segment of the ninth rib in the posterior axillary line was removed and closed thoracostomy drainage established. Approximately 150 cc. of cloudy fluid was removed at the time of rib resection. The appearance of saliva and ingested methylene blue in the thoracostomy drainage indicated that an esophagopleural cutaneous fistula had been established. The small apical pocket that remained was aspirated on three occaxions with removal of from 15 to 20 cc. of serous fluid each time. Following aspiration a solution containing 300,000 units of penicillin was instilled. Re-expansion of the lung was practically complete by the fifth day after therapy was begun, and within two weeks the esophageal fistula had closed and the catheter was removed (fig. 5 b).

Comment: That the esophageal fistula was draining into the right apex was apparent from roentgenograms taken on the fifth postoperative day. The enzyma-

tic agents broke up this apical pocket and allowed the esophageal drainage to accumulate at the base where external drainage could be established. Alterna-

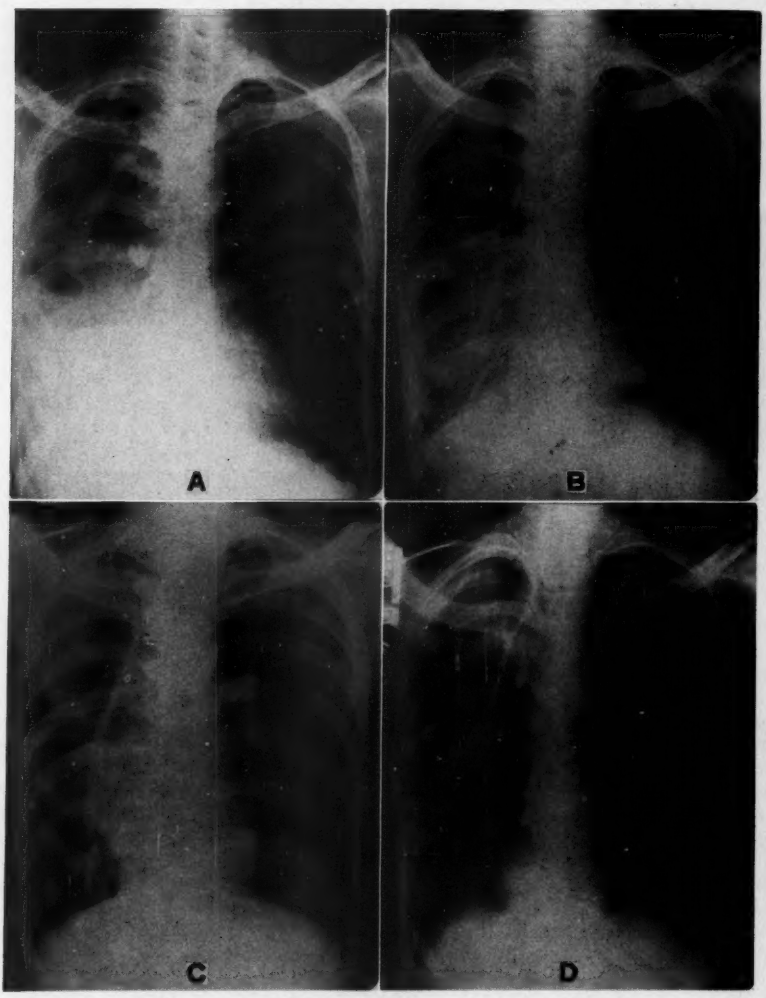

FIG. 6. Case 15. Postesophageal resection empyema. Roentgenograms (a) on eighth postoperative day showing fluid loculations in right side of chest. The barium deposit at level of the seventh rib lies posterior to the stomach and established the presence of an esophagopleural fistula, (b) after one week of SK-SD therapy, and removal of 1850 cc. of fluid, (c) two months, and (d) four months after enzymatic therapy.

tively, open thoracostomy and manual removal of the locules of fluid would have been required.

Case 15. E. B., a man 34 years old, swallowed lye in an attempted suicide. Gastrostomy and retrograde bouginage of an esophageal stricture were unsuccessful. On March 5, 1951 the gastrostomy was closed and esophageal resection and esophagogastrostomy were performed, separate right thoracic and midline upper abdominal incisions being employed. On the eighth postoperative day fever, dyspnea, and right thoracic pain developed, and roentgenograms revealed the presence of fluid in the right side of the chest. A roentgenogram following administration of lipiodol confirmed the suspicion of an esophagopleural fistula (fig. 6a). A no. 24 catheter was inserted in the eighth interspace posteriorly through which 180,000 units of SK and 100,000 units of SD were placed intrapleurally. Eighteen hours later the catheter was opened and 600 cc. of dark, thin fluid removed. Streptokinase-streptodornase solution was placed into the right pleural space daily for the next two days and 450 cc. of fluid was aspirated via the catheter. As roentgenograms had indicated a large fluid collection anteriorly, an intercostal catheter was inserted through the fifth interspace in the midclavicular line and the posterior catheter was removed. The prompt appearance in the catheter of ingested methylene blue indicated that an esophagopleural cutaneous fistula had been established (fig. 6 b). On March 19 a jejunostomy was performed for feeding. During the succeeding two weeks the drainage from the catheter averaged more than 150 cc. daily and contained large amounts of chloride and potassium so that intensive fluid and electrolyte replacement was required. With radiopaque material in the stomach, roentgenograms indicated complete pyloric obstruction, which was relieved by operative mobilization of the pylorus. The drainage from the catheter in the chest then steadily diminished and on May 5 the catheter was removed (fig. 6 c). The esophageal leak had closed sufficiently to permit a regular diet by mouth. Roentgenograms revealed almost complete re-expansion of the lung; the patient had become ambulatory and was steadily improving (fig. 6 d) when, five months after esophagogastrostomy, he suddenly died. The suspicion of pulmonary embolism as the cause of death was not confirmed, since autopsy was not permitted.

Comment: Despite its tragic ending, an effective esophagopleural cutaneous fistula was established in this case, the lung re-expanded, and the intrapleural infection was eradicated without resort to open thoracostomy. In this respect enzymatic therapy was successful. The danger of using a broad-spectrum antibiotic prophylactically is again emphasized. The simultaneous elimination of the usual gram-positive and gram-negative pathogens was followed by an infection with Bacillicus proteus, but fortunately this organism was sensitive to chloromycetin.

2. Clotted Hemothorax

Most cases of traumatic hemothorax encountered in civil practice result from stab wounds of the chest. Such wounds are usually small and pulmonary parenchymal damage is minimal. As a consequence 90 per cent to 95 per cent of these cases can be managed successfully by needle aspiration. In the remaining 5 per cent to 10 per cent intrapleural clotting occurs and aspiration becomes ineffectual. Under these circumstances when the clot is small and produces minimal interference with pulmonary function, no further therapy is indicated since resorption will take place. When the clotted hemothorax is of sufficient size to reduce pulmonary function significantly, or the coagulum becomes infected, additional therapeutic measures must be employed. To this relatively small group of cases surgical decortication has been applied with considerable success.

The ability of SK-SD to liquefy the fibrinous coagulum in clotted hemothorax

has been well demonstrated, but the extent to which these agents reduce the need for surgical decortication has not been definitely determined. In an effort to evaluate enzymatic pleural debridement critically, we have attempted to restrict use of SK-SD to those cases of clotted hemothorax which might otherwise be considered for surgical decortication.

Eighteen patients with clotted hemothorax have been treated with SK-SD (Table 2). In 17 the hemothorax was traumatic in origin, and in the other it resulted from attempted extrapleural pneumothorax for pulmonary tuberculosis. Of the traumatic cases, 8 were stab wounds of the chest, 7 gunshot wounds, and

TABLE 2

Results of SK-SD therapy in 18 patients with hemothorax

Pt. No.	Type Injury	Duration (days)	Injection SK-SD	Fluid Removed (cc.) at Thoracentesis		Results		
			Days of Therapy	Last Pre-SK-SD	First Post-SK-SD	Succ.	Part. Succ.	Unsucc.
17	Stab	13	1	5	400	X		
18	Crush	21	4	100	225	X		
19	Gunshot	13	4	5	350	X		
20	Gunshot	3	6	250	500	X		
21	Stab	34	1	40	95			X
22*	Crush	25	5	250	475	X		
23	Gunshot	15	2	75	1200	X		
24	Stab	24	2	215	600	X		
25*	Gunshot	5	6	10	500	X		
26	Gunshot	10	1	150	400	X		
27	Extra-pleural pneumo.	14	2	50	200	X		
28	Stab	7	1	5	1000	X		
29	Gunshot	20	3	100	140		X	
30	Stab	18	2	90	550	X		
31	Stab	13	1	50	680	X		
32	Stab	9	9	200	450	X		
33*	Stab	10	2	100	400			X
34	Gunshot	3	2	150	600	X		

* Hemothorax infected.

2 crushing injuries with multiple fractured ribs. The interval between injury and enzymatic therapy varied from 3 to 35 days with an average of 14 days, and generally represents the period during which simple thoracentesis was attempted.

In three instances the hemothorax was infected, and in the 2 cases in which enzymatic therapy was continued to completion it had to be vigorously applied for satisfactory results.

The number of injections (days of therapy) of SK-SD varied from one to nine and did not appear to be related either to the duration or the size of the hemothorax. In some instances a massive intrapleural clot became liquefied after only one application of SK-SD (case 28) whereas in others multiple applications were necessary before fluid in the thoracic space was completely evacuated (case 32).

All patients received antimicrobials systemically, either penicillin alone or combined with streptomycin, while being treated with SK-SD.

In every instance in which therapy was successful, the amount of fluid removed after the intrapleural placement of SK-SD solutions was significantly greater that the amount removed at the last thoracentesis prior to therapy. This increase was principally a result of liquefaction of fibrin clot, but a small increment was probably derived from an outpouring of serum from pleural surfaces in response to the enzymatic agents.

The criteria for success of enzymatic treatment of clotted hemothorax are (1) removal of significant amounts of fluid from the involved thoracic space after

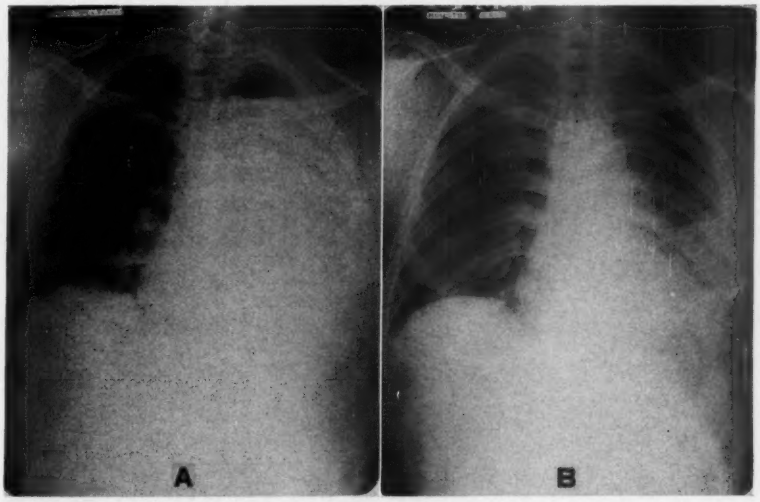

FIG. 7. Case 28. Clotted hemothorax—Roentgenograms (a) prior to injection of SK-SD, and (b) 24 hours later, after removal of 1000 cc. of fluid.

intrapleural placement of SK-SD when prior thoracenteses have been ineffectual, and (2) clinical and roentgenographic evidence of evacution of the pleural space. Since roentgenographic clearing lagged behind clinical improvement, particularly in the group of gunshot wounds in whom intraplumonary hemorrhage was a significant factor, it could not be relied upon entirely as a guide to therapy.

Of the 18 patients treated, in 15 therapy was considered successful, in 1 partially successful, and in 2 unsuccessful (Table 2). The failure in case 21 was undoubtedly a result of inadequate therapy of a hemothorax that had been present for 34 days. In case 33 enzymatic therapy was abandoned when thoracostomy became necessary for repair of a diaphragmatic hernia resulting from the stab wound. In case 29 treatment was considered only partially successful because the clot was not completely removed, as evidenced by lack of roentgenographic clearing for several weeks following therapy.

The following case reports illustrate the methods employed in treating clotted hemothorax with SK-SD solutions:

Case 22. T. C., a Negro man aged 28 years, sustained a stab wound on the left side of the chest with resultant hemothorax. Thoracentesis on admission yielded 400 cc. of blood but roentgenograms the following day revealed that the blood had reaccumulated (fig. 7 a). Repeated attempts at aspiration were unsuccessful. A solution of 200,000 units of SK with 100,000 units of SD was injected at two sites on the left side of the chest. Twenty-four hours later thoracentesis yielded 1000 cc. of sanguineous fluid and roentgenograms revealed almost complete clearing (fig. 7 b).

Case 23. H. H., a Negro man 38 years old, received a gunshot wound of the right side of the chest and sixth thoracic vertebra with resulting right hemothorax and paraplegia.

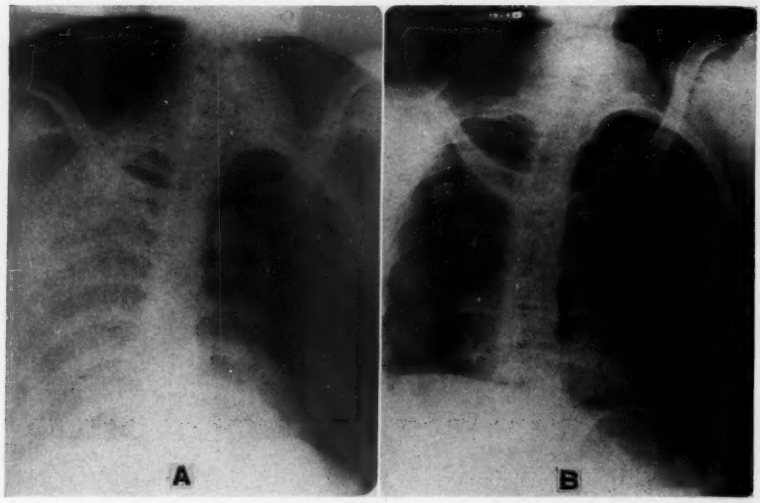

FIG. 8. Case 23. Clotted hemothorax—Roentgenograms (a) just prior to injection of enzymatic solution, and (b) 48 hours after second injection of SK-SD and removal of 1600 cc. of fluid.

Fourteen days after injury there was still a thick coagulum which resisted efforts at aspiration (fig. 8 a). A solution of 100,000 units of SK and 50,000 units of SD was injected through an interspace, and at the end of 18 hours 1200 cc. of dark blood was removed. Streptokinase-streptodornase solution was injected a second time in the same dose and after aspiration complete clearing of the chest occurred (fig. 8 b).

Comment: The prompt liquefaction of the sanguineous coagulum which occurred in these 2 cases is characteristic of the response to intrathoracic use of SK-SD obtained in the majority of cases of massive clotted hemothorax.

3. Miscellaneous

Nine patients with intrapleural fluid collections other than purulent and sanguineous have been treated with SK-SD (Table 3). In cases 35 and 36 an encapsulated serosanguineous effusion prevented re-expansion of the lung following

lobectomy. The intrapleural application of the enzymatic agents made possible evacuation of fluid from the thoracic space, and the lung promptly re-expanded. In case 37 multiple apical fluid levels and elevation of temperature developed on the seventh day following left lower lobe pulmonary resection. A solution of SK-SD injected into one of the loculations after aspiration made possible removal of a considerable amount of serous fluid from the apex, and although two small fluid levels persisted, the lung re-expanded and the temperture returned to normal.

During the immediate postoperative period following partial pulmonary resection when lung re-expansion is hindered by loculated fluid, or clot, or when empyema develops, enzymatic therapy may be used to advantage. In cases 35, 36 and 37 SK-SD therapy was cautiously employed because of the potential

TABLE 3

Results of SK-SD therapy in 9 patients with miscellaneous thoracic conditions

Pt. No.	Diagnosis	Injections SK-SD Days of therapy	Results		
			Succ.	Part. Succ.	Unsucc.
35	Encapsulated effusion, postlobectomy	1	X		
36	Encapsulated effusion, postlobectomy	1	X		
37	Encapsulated effusion, postlobectomy	1		X	
38	Loculated effusion, secondary to metastatic malignancy	2			X
39	Loculated effusion, secondary to metastatic malignancy	2			X
40	Spontaneous pneumothorax, failure re-expansion	2	X		
41	Loculated effusion, etiology unknown	5	X		
42	Loculated effusion, etiology unknown	1			X
43	Loculated effusion, etiology unknown	1	X		

threat to healing of the hilar structures in this early postoperative period. However, it is probable that when pulmonary resection is properly done, particularly as regards pleuralization of the bronchus, the fibrinolysis initiated by SK will not interfere with the healing process.[4]

Patients 38 and 39 had massive effusions with collapse of the lung. Repeated thoracenteses had failed to remove the fluid completely. Intercostal catheter drainage and topical use of SK-SD solutions resulted in partial re-expansion of the lung. However, the effusions were found to be due to pleural extension of bronchogenic carcinoma, so enzymatic therapy was abandoned. In case 40 right spontaneous pneumothorax with 50 per cent collapse of the lung developed. Serosanguineous effusion was removed by thoracentesis, but the lung did not re-expand. Intercostal catheter drainage and use of SK-SD twice during a period of three days resulted in prompt pulmonary re-expansion. It has been noted during surgical decortication for persistent pulmonary collapse following recent spontaneous pneumothorax that the lung is often held captive by a thin fibrinous pleural rind which separates easily from the surface of the lung. The large

quantity of fluid removed and the rapid pulmonary re-expansion after employment of SK-SD in this case suggests that such a fibrinous exudate was responsible for the continued collapse and warrants trial of these agents in the treatment of refractory spontaneous pneumothorax. Whether pleural symphysis will result from such therapy has not been determined.

In patients 41, 42 and 43 loculated pleural effusions of undetermined etiology were treated with SK-SD. In cases 41 and 43 the effusions were successfully aspirated after the intrathoracic injection of SK-SD. In case 42 therapy was not initially successful and the patient left the hospital before additional treatment could be given.

SUMMARY

In this series, 10 (62.5 per cent) of 16 patients with thoracic empyema were successfully treated by use of SK-SD and in 2 (12.5 per cent) therapy was partially successful (Table 4). The promptness with which multiple purulent locules were broken up in post-pneumonic empyema, and the liquefaction of the infected coagulum which occurred in the post-pneumonectomy infections, indicate strikingly the effectiveness of the enzymatic agents in the therapy of these conditions. Three of the four failures (25 per cent) were in patients with chronic, tuberculous empyema and serve to emphasize the relative ineffectiveness of SK-SD when the pleural exudate is of long duration and fibrous tissue replacement has occurred. Under these circumstances surgical decortication is preferred if pulmonary re-expansion is desired.

Of 18 patients with clotted hemothorax, therapy was successful in 15 (83.3 per cent), partially successful in 1 (5.5 per cent), and unsuccessful in 2 (11.1 per cent) (Table 4). These results are especially significant since SK-SD therapy was reserved for the most severe cases. It would seem that SK-SD therapy is, except in rare instances, an adequate substitute for surgical decortication in the management of complicated hemothorax encountered in civilian practice.

A group of 9 additional patients with pleural collections, of which fibrin was the major substrate, was treated with these enzymatic agents. In 5 (55.5 per cent) therapy was successful, in 1 (11.1 per cent) partially successful, and in 3 (33.4 per cent) unsuccessful (Table 4).

TABLE 4

Summary of results of SK-SD therapy in 43 patients with thoracic conditions

Type	No. Pts.	SK-SD Therapy					
		Succ.		Part. Succ.		Unsucc.	
		Cases	%	Cases	%	Cases	%
Empyema	16	10	62.5	2	12.5	4	25
Hemothorax	18	15	83.3	1	5.5	2	11.1
Miscellaneous	9	5	55.5	1	11.1	3	33.4
Totals	43	30	69.8	4	9.3	9	20.9

The results of SK-SD therapy in 3 patients following partial pulmonary resection, and in 3 following esophageal resection suggest that these agents may be useful in the management of certain pleural deposits which occur in the early period after thoracic surgical procedures.

On the basis of these observations and the experience of others, it appears that SK-SD have a definite role in the management of pleural exudates. These agents may be useful to the thoracic surgeon either as an ancillary measure to surgical attack, or their use may preclude operative therapy entirely. Only through careful evaluation of the problems presented by each case and adherence to sound surgical principles of management will their maximum effectiveness be realized.

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INOCULATION AMEBIASIS CUTIS—A CASE REPORT*

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Since 1891 amebic ulceration of the skin has been recognized as a specific type of chronic gangrene, which, although rare, has been reported by more than occasional observers practicing in regions in which amebiasis is found.[2, 13]

A survey of the reported cases reveals that skin lesions of amebiasis may be placed in three groups:[4]

1. Amebic ulcerations of the skin and body wall, secondary to a spontaneous or surgical opening of a visceral lesion, such as a hepatic abscess, amebic appendicitis, or colostomy in the presence of amebic colitis.

2. Infection and ulceration of the perianal region from the discharges of amebic colitis.

3. Amebic ulceration arising without any direct extension from a visceral lesion. (The "amebiasis of inoculation" of Tourraine.)

There is a possible fourth group: amebic dermatoses, skin lesions, secondary to intestinal amebiasis, without cultural properties of endameba histolytica but apparently cured upon arresting the primary disease. This group is one not quite recognized in the United States, but Pierini and Borda[11] have reported 16 cases of nummular eczema, 13 of which showed endameba histolytica in the stool examinations. The first two types of amebiasis cutis have formed the bulk of the cases reported. These have been fully covered in a review by Wyatt and Buchholz.[13]

It is the *inoculation* group of cutaneous amebiasis, gangrenous ulcers of the skin without any direct connection with the viscera, that are considered in this report. Engman and Heithaus[3] describe discrete and disseminated lesions of the skin in a child with intestinal amebiasis, plus bullous impetigo. Auto-inoculation by scratching resulted in areas of superficial gangrene, having the characteristic description of amebic gangrene, and showing endameba histolytica by smear and biopsy specimens. Despite emetine and various local treatments, this patient died. Hausen and Stark[6] reported the case of a woman 59 years of age with black and punched-out gangrenous ulcers on the anterior portion of the leg and intestinal amebiasis. The lesions occurred after trauma to the leg in a blackberry patch, and were presumably inoculated with amebae, although no culture or biopsy specimen from the lesions was obtained. These lesions were cleared with saline dressings and emetine.

Because of the increasing recognition of amebiasis in this country and the larger number of our troops stationed in tropical countries during the war, publication of this case was withheld with the hope of presenting a series rather than a case report. Since no similar case has come to our attention during the intervening 10 years and because of the rarity of this inoculation type of amebic ulceration of the skin, we are now presenting it.

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CASE REPORT

M. D., aged 48 a rural laborer from Indiana, was admitted to the Veterans Hospital, Hines, Illinois on July 28, 1939, for treatment of carcinoma of the abdominal wall. This emaciated white man, who weighed 110 pounds, appearing acutely ill with rapid shallow costal respirations, gave a history of progressive ulceration of the abdominal wall for 2 years, with ingravescent weakness pain and dyspnea despite all medical treatment. His abdominal wall was the site of a large, foul-smelling, circular, necrotic ulcer, extending from the xiphoid to below the umbilicus. A deep red indurated area circumscribed the ulcer for a

FIG. 1a

FIG. 1. a) Aug. 5, 1939, appearance of lesion at onset of treatment. b) Sept. 12, 1939, one week after onset of zinc peroxide dressings. Note blind soft tissue sinus on the left. c) Appearance Nov. 28, 1939. Patient refused skin graft. d) Feb. 23, 1940, spontaneous healing prior to discharge.

distance of 5 cm. In the midline, to the left of the ulcer, were two deep sinuses extruding thick, green, offensive pus. The ragged, slightly raised margin of the ulcer extruded pus on pressure, and the entire lesion was very tender to touch. The irregular, deep base was formed to foul necrotic tissue, and extended to a depth of 3½ cm. below the plane of the abdominal wall in several places (fig. 1-a). The sinuses to the left of the wound were probed to 4 cm. laterally and downward, and necrotic tissue was encountered. Lipiodol injected repeatedly into the sinuses pooled in the soft tissues of the abdominal wall and no visceral connections could be found. Roentgenographic examination of the lungs was negative for any recent or old pathologic changes.

On Aug. 2, 1939, a biopsy specimen (fig. 2) was removed from the lateral abdominal wall, and described by Dr. Robert Shreck as follows: "The tissue has a large area of necrosis. Imbedded in the necrotic tissue is a large number of large, round or oval cells, with consider-

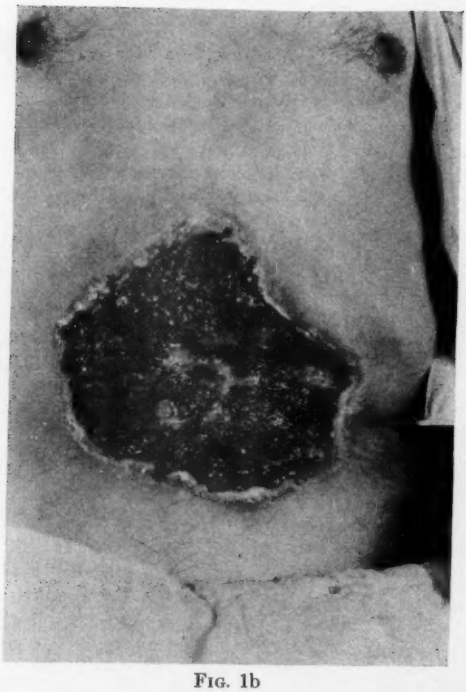

FIG. 1b

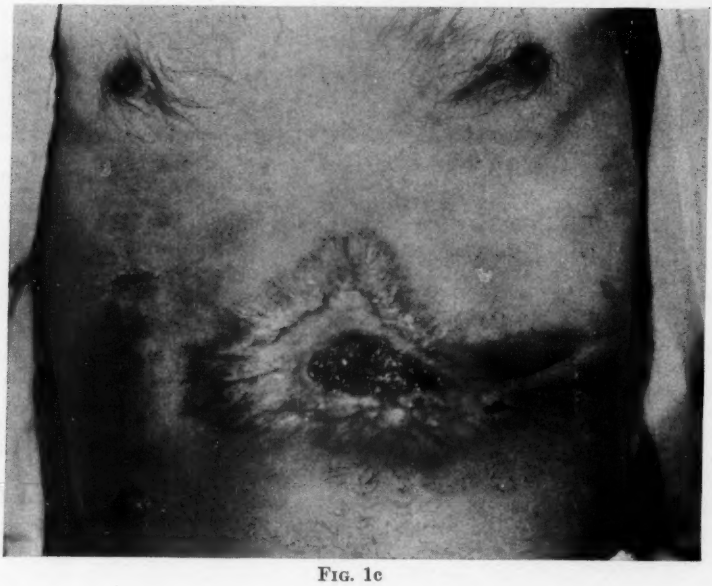

FIG. 1c

able amount of granular cytoplasm. The nuclei of these cells are small and hyperchromatic. A few cells have phagocytized material. An occasional cell has pseudopedia and clearly defined ectoplasm. Adjacent to the necrotic debris are young granulation tissue and atrophic striated muscle fibres. Numerous lymphocytes infiltrate the granulation tissue. There are also a few large cells similar to those seen in the necrotic area within the visible granulation tissue. These large cells are endamoebae histolytica. The diagnosis is amebiasis cutis."

Study of the pus from the abdominal ulcer showed a motile cell resembling an ameba, with many red blood cells present. A *direct smear* showed many long-chain streptococci, gram negative curved organisms, and gram positive cocci arranged in single formation. Wright's stain showed many red blood cells with gram positive diplococci imbedded in them. *Aerobic cultures* showed a growth of gram positive diplococci or blood agar, producing no hemolysis, and some gram negative bacilli. Fermentation occurred in lactose media.

FIG. 1d

Repeated anaerobic cultures revealed long-chain nonhemolytic streptococci and B. coli. A section taken from the deep portion of the reddened area was cultured anaerobically and grew nonhemolytic streptococci.

Under intensive treatment with emetine, the patient's general condition improved, but the wound remained foul and necrotic. Activated zinc peroxide dressings were then applied daily, after the method of Meleney,[10] and sulfonamide given by mouth in an attempt to eradicate the streptococcic infection. Immediately the reddened area disappeared, and the necrotic wound showed clean granulations. After packing with zinc peroxide this sinus healed uneventfully. As shown in the figures, improvement was rapid and marked under this combination of emetine, sulfonamide, and zinc peroxide local dressings. Weight and strength returned and the patient was discharged. A photograph taken on Feb. 23, 1940 (fig. 1-d) shows the complete healing of the lesion without skin grafting.

After the diagnosis of amebiasis cutis was established by histologic study, a careful history revealed that the patient, during World War I, was in service at a Texas cavalry post, which, records show, was heavily infected with amebiasis.[1] Although the patient

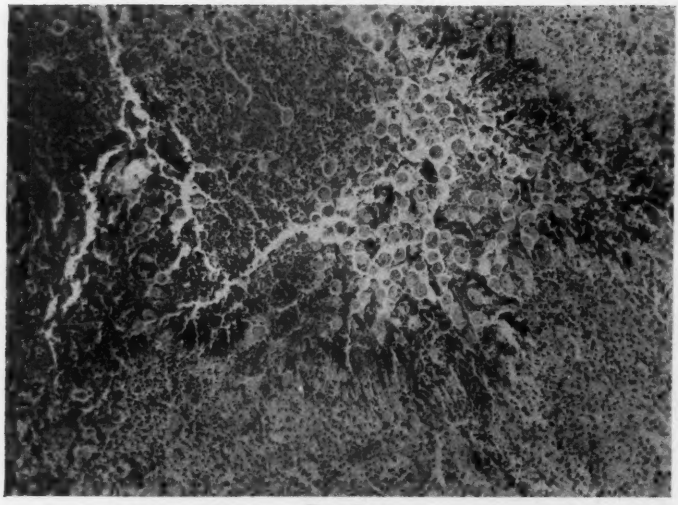

FIG. 2a

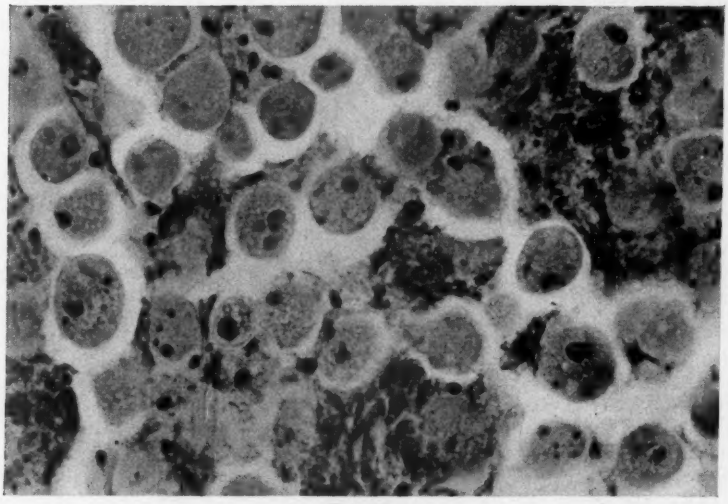

FIG. 2b

FIG. 2. a) Biopsy specimen of lesion, low power (described in text). b) Biopsy specimen of lesion, high power (described in text).

stated that he had an attack of dysentery 20 years ago during his Army career, he insist that for the past 20 years he had not had a diarrheic movement. Further questioning revealed that in 1937, two years before his admission, the patient had struck himself while shovelling coal and noticed an abrasion of the abdominal wall. This ulcerated slowly and, not withstanding all local treatments grew to the size seen on admission.

COMMENT

Characteristics of this lesion are similar to those found by other authors[9] in describing cases due to secondary infection following drainage of internal amebiasis, including the advancing halo beyond the margin of the ulcer, which varied in color from a dusky red until it merged with the color of the normal skin. It is believed by Meleney[8] that the most important factor in care of amebic ulceration of the skin is the early administration of emetine, and then a thorough debridement of the involved tissue. Such a debridement done in an emaciated person entails the removal of a tremendous amount of tissue and produces a large amount of bleeding. In our case, no such debridement was done except in the course of the daily zinc peroxide dressing. Convalescence would have been shortened by skin graft, which the patient steadily refused.

In these few reported cases of amebic ulceration without evidence of a direct connection with an internal focus, as the case reported by Engman and Heithaus as well as ours, it appears as if the ameba must be preceded by an infection with other organisms, and the resultant necrosis is due to a synergistic action between the bacteria and the protozoa.[7] Gauducheau[5] in 1916 recognized that virulence in his case must have been ascribed to an associated bacteria. Although bacteriologic reports are scarce, mention is made of the streptococci, staphylococci and colon bacillis found in association with ameba during recent cases involving intestinal lesions. We believe that without the zinc peroxide used locally, in the treatment of our case the patient would never have recovered as these were the preantibiotic days.

SUMMARY

A case of amebic gangrene of the skin of the anterior abdominal wall has been presented. It is believed that this is one of the few cases of inoculation amebiasis cutis without any direct connection with the viscera. Biopsy specimens of the lesion revealed endamoeba histolytica, which were corroborated by stool findings and wound cultures. At the same time anaerobic streptococci were cultured from the wound secretion. Under emetine, sulfonamide and zinc peroxide dressings locally, without debridement, the wound granulated and healed without skin graft.

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THE VALUE OF SERIAL STUDIES OF CEREBROVASCULAR PERMEABILITY WITH RADIOACTIVE IODINATED SERUM ALBUMIN AND THE SCINTILLATION COUNTER, PARTICULARLY IN THE DETECTION OF NEUROSURGICAL LESIONS

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Before the advent of radioactive isotopes, the blood-brain barrier or cerebrovascular permeability, had been studied routinely with uranin, which is sodium fluorescein, as long ago as 1920, at which time Katzenelbogen[10] noted that the permeability was increased in certain types of diseases, such as central nervous system syphilis and epidemic cerebrospinal fluid meningitis. In 1943, Sorsby, Wright, and Elkeles[13] utilized other dyes in vital staining in brain surgery. In the following year, Aird[1] and his associates also studied the protective barriers of the central nervous system with sodium fluorescein, and noticed an increased permeability in certain epileptics, infections, and post-traumatic diseases of the central nervous system. He, too, with these nonradioactive isotope means, noticed impairment of the blood cerebrospinal fluid barrier after such procedures as pneumoencephalography, spinal anesthesia, and ventriculography. A most detailed survey and analysis of disorders of cerebrovascular permeability have been performed by T. Broman[5] and his Swedish cohorts since 1938, utilizing mainly the dye trypan blue in various lesions such as trauma, multiple sclerosis, and intracranial tumors as well.

These studies were greatly simplified when Moore[11, 12] first used radioactive diiodofluorescein in the diagnosis and localization of brain tumors in 1948. By a progressive modification of the technic of external localization[8, 3], and the use of automatic devices, and more recently, the use of a scintillation counter, an increasing accuracy of localization of intracranial lesions has been obtained. The recent acquisition of a newer radioactive isotope which is not a vital dye but a normal component of human serum (namely, radioactive iodinated albumin[7]) has added greatly to the possibilities of these external localization studies.

We, here, have further extended and improved the technic of the radiodye test by the use of a modified scintillation counter[2] which is up to 100 times more sensitive than the originally used Geiger-Mueller tube, or even the newer more sensitive bismuth cathode tubes. Because of the greater precision and sensitivity of the scintillation counter, not only has the dose of radioactive isotopes been reduced, but the actual testing time has also been reduced to 20 to 40 minutes, as contrasted to the 2½ to 4 hours previously required when using conventional Geiger-Mueller tubes,[3] and the 1 to 1½ hours required by bismuth cathode Geiger-Mueller tubes.[9]

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INSTRUMENTATION AND TECHNIC

The radiation detection equipment consists of a wide-angled scintillation counter (which Allen[2] has proved to be of such value in his studies on the thyroid gland), adequately shielded with lead and tungsten, and mounted for maximum flexibility on a dental x-ray stand. The scintillation counter is connected by a preamplifier into a highly modified counting rate meter, and the counts are finally recorded automatically on an Esterline Angus milliammeter, and also on a decade scaler, at a preset time interval of one-half a minute.

With the use of radioactive iodinated human serum albumin, we have found a fuller scope in the possibility of re-examining the same lesion at various intervals of time following the injection. The minimal 32 readings in the supra and infratentorial regions of the skull, as also the midline readings, are again carefully taken symmetrically, with each reading being only of one-half minute duration. Whereas previously a minimal reading of three minutes was required with the Geiger-Mueller counter[3] (and usually this amounted to more, since a plateau of such three minutes' length might at times take seven to eight minutes), now, with this very sensitive scintillation counter, a thirty-second reading gives counts in such a high range that statistical accuracy is obtained in this relatively short period of time. The use of the scaler also adds to the accuracy, and dispenses with previous visual graphic calculations, thereby dispensing with another source of *probable error*. The actual time of testing is approximately 20 to 40 minutes, including the time of checking all abnormal positions. This is a great boon over the older method, where from 2½ to 4 hours were consumed in reading with radioactive diiodofluorescein and a Geiger-Mueller counter.

Radioactive Albumin vs. Diiodofluorescein: Because radioactive iodinated human serum albumin (RIHSA) remains in the blood stream for at least eight days with approximately 50 per cent still being present on the third day, confirmation studies of focal lesions can still be made on the first, second, and even third days following the injection. One of the greatest disadvantages of the diiodofluorescein technic was the fact that this *foreign body* dye rapidly leaves the cerebral circulation and is excreted by the liver, mainly within the first 24 hour period. The greatest source of error[4] with this diiodofluorescein method has been in *not* reading between three-quarters of an hour after injection and, at the latest, two hours after, when the best concentration time has occurred. Any readings after this time has only been pertinent for checking purposes, since the concentration is rapidly receding following this interval of time. By contrast, utilizing RIHSA, a wider range, particularly as regards timing, is permitted and adequate resource to frequent rechecking is possible, not only at the time of initial reading, but also for rechecking at frequent intervals in the next 72 hours. This latter is of great importance, particularly in borderline cases.

Because of the markedly increased sensitivity of the recording apparatus now used, a great deal of emphasis must again be placed on very accurate positioning, as described in previous articles.[3, 8] Each of the minimal 32 positions has its own normal standard readings, which vary from their symmetrical positions, usually

well within 6 to 7 per cent of the counts per minute.[9] The more accurate one is in the symmetrical positioning of the tube, the closer to a 1 per cent, or less, difference in readings from side to side, is possible (fig. 1). For greater accuracy, we are now using a skin pencil and compass to mark symmetrical positions on the scalp. From our present experience we have learned that tumors usually show at least a 10 per cent difference in symmetrical position, and more frequently from 15 per cent to 40 per cent, depending upon the cellularity and vascularity of the lesion (figs. 1, 2). For pituitary, brainstem, and posterior fossa lesions, we still

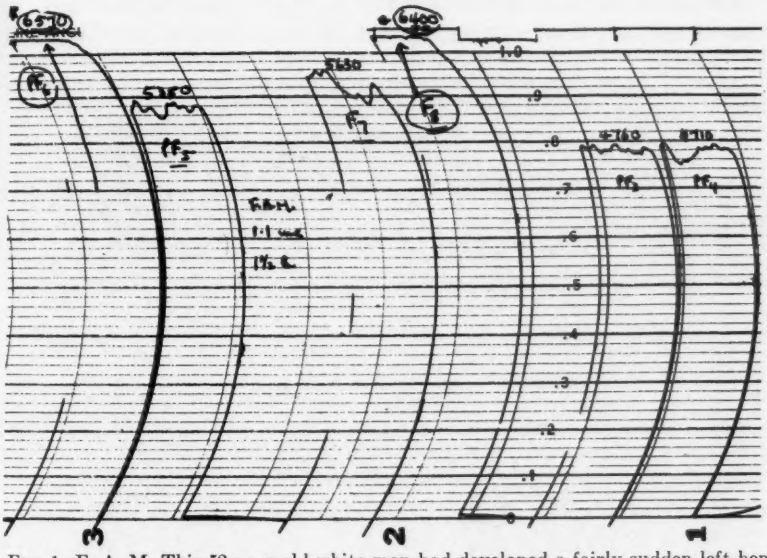

FIG. 1. F. A. M. This 52-year old white man had developed a fairly sudden left hemiparesis which was felt to be on a cerebrovascular basis. The two symmetrical prefrontal positions are well within normal limits with a difference of only 50 counts per minute which is only about a 1 per cent variation. However, the adjacent right PF-6 position reads 6570 c.p.m. as against the left postero-inferior frontal reading of 5350, which is a difference of 1220 counts per minute, or more than 20 per cent variation. The right anterior temporal, or F-8, position reads 6400 c.p.m. on the scaler, a difference of 770 c.p.m. These readings are significant of a cellular vascular lesion in these areas. This record shows that the focus did not extend to the prefrontal region as manifested by the very equal PF-3 and PF-4 readings.

prefer the radiodye method, since we have a much larger series of normal variations for the appropriate midline positions than we have for radioactive albumin.

The Significance of Serial Studies: Because of the short stay of diiodofluorescein intracranially, it was impossible to do more than a static study of any lesion, be that neurological or neurosurgical. Fortunately, with the use of the more versatile RIHSA, we have been able to adopt a *dynamic* approach to the study of intracranial lesions. This has yielded us a great deal more information about the progressive nature of lesions, such as might be compared to the value of *tolerance tests* recently devised in studying both liver and kidney and pancreatic functions as compared to, for example, the use of just a single blood sugar determination,

instead of a glucose tolerance curve. The analogy can be carried even further to emphasize, especially, the time factor in these instances.

In several equivocal cases following the use of diiodofluorescein, where the readings were so close to our recognizable normal ranges, that a diagnosis of *normal radiodye record* had been given, the test was repeated with RIHSA, which yielded beautifully outlined focal lesions. One of these recent cases was a middle-aged man with a peptic ulcer syndrome of recent onset who, in the presence of a negative upper gastrointestinal series, was being treated for his *hyperacidity* by an internist. However, with the advent of hallucinations of a queer taste and peculiar smell, and also some definite though minor personality changes, the

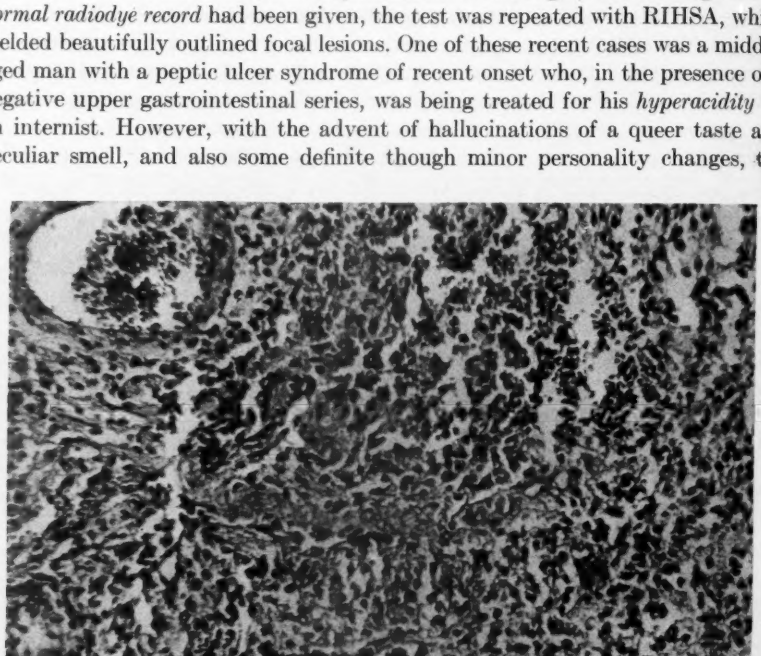

FIG. 2. This is the glioblastoma multiforme removed at surgery from patient, F. A. M., in figure 1. The cellularity, multiformity, and disturbed angioarchitectural patterns are well exemplified and are the cause of the disturbed cerebrovascular permeability or blood-brain barrier permeability changes.

patient was transferred to the care of a psychiatrist for what was believed to be a functional ailment. Despite a relatively negative neurological examination and skull roentgenograms, a slightly abnormal electro-encephalogram focus caused enough suspicion so that a radioisotope localization study was requested. The radio-fluorescein study was done an hour following the injection and proved to be entirely non-revealing. A repeat study about two weeks later with RIHSA revealed a slight focus with a less than 10 per cent pertinent dlfference noted in the right postero-inferior frontal and superior temporal regions, with the rest of the readings being well within normal limits. The six-hour survey revealed this same focus to be more marked with differences now ranging between 12 and 15 per cent. However, again the surrounding regions were well within normal limits.

Interestingly enough, the 24 hour reading revealed a tremendous focal uptake of radioactive isotope centered in the above region, but spreading peripherally to involve most of the superior and inferior temporal gyri, as well as the posterior portion of the orbital surface of the frontal lobe and extending posteriorly also toward the parieto-occipital areas at the periphery of the Sylvian fissure. The focal symmetrical differences with this same injection of 300 microcuries of RIHSA now showed differences at the heart of the lesion, ranging from 20 to 80 per cent over the opposite side. At surgery, we were able to verify the size and extent of this lesion, which proved to be a rapidly infiltrating glioblastoma multiforme. With the further use of RIHSA, this patient was followed at frequent intervals following major resection and internal decompression of his lesion, until his death, where again we were able to verify these focal studies.

In certain instances we have found the exact opposite to be true as well, where the six-hour reading following injection of RIHSA outlined the lesion very adequately, whereas the 24 and 48 hour readings were only moderately confirmatory. These preliminary serial studies have revealed that there is an *optimum time* for uptake in various lesions of the brain including most of the major types of brain tumors such as glioblastoma, astrocytoma, pituitary tumor, and metastatic tumors. Each of these will vary not only in the manner of uptake of the radioactive isotope, but particularly as regards the time of uptake, varying with the microscopic degree of anaplasia, necrosis, and angio-architectural pattern.

In metastatic tumors, for example, where nodules of varying age and evolution and cellularity and vascularity and necrosis occur simultaneously, a certain few of these nodules will have a most outstanding radioactive isotope uptake at the six-hour survey; whereas those with more central necrosis show the greater uptake of radioactive albumin at the 24 and even 48 hour intervals following the injection. This latter feature has actually been noted by many investigators since the beginning of this century, by the use of nonradioactive means such as vital dyes[5, 6, 13] when gross visual discoloration of the central necrotic cavities of tumors has been noted from one to three days following the administration of the vital dye. It appears that in the absence of tumor capillaries in these necrotic areas, the vital dye has to *seep in* from the more active tumor cellular periphery, and, for the same reason, has greater difficulty in being reabsorbed into the general circulation. Other factors entering into consideration in these serial studies, are the degree of microscopic angio-architectural differences, vascular stasis, or arteriovenous shunts, especially within such tumors as glioblastomas and metastatic carcinomas.

Dynamic vs. Static Studies: With this dynamic approach, we have recently begun some studies on the toxic effects upon cerebrovascular permeability by agents such as 35 per cent diodrast by performing pre and postangiographic studies. Our preliminary studies confirm the fact that these substances are moderately toxic and cause perceptible changes in the blood-brain barrier for varying lengths of time.

With these serial studies, we have been able to study the effects of various epileptic phenomena and the changes in permeability created by them. We have

learned that following a major seizure, changes may be present up to two to three weeks following such ictal phenomena. Hence, it is important to know the date of such seizures, since otherwise minimal but very definite increases in uptake will occur which will yield *false positives*. If such a lesion shows either the same uptake, or an increased uptake three weeks following the seizure, then our studies have usually shown that a progressive lesion such as a tumor exists, whereas if the opposite occurs, the lesion is more likely a vascular or non space-occupying one. This has been one of the main sources of errors in previous studies where only one reading was undertaken.

Subdural hematomas and craniocerebral injuries show a varying uptake which is never as highly differential as in the more cellular tumors, but which do vary a great deal with the age and duration of these traumatic lesions. The more actively vascularized ones show the greatest degree of permeability changes, and therefore of radioactive isotope uptake. In a recently verified right frontal subdural hematoma of three months duration, the anterior frontal area where the membrane was thickest and the granulation tissue the most marked, a well-defined focal uptake was noted, which was difficult to distinguish from readings of a tumor or abscess. The central portion of this later verified encapsulated hematoma showed readings which were almost equal to that of the other side and in some instances slightly lower. The focal uptake was very accurate, though the microscopic diagnosis could not, of course, be ascertained, it was felt that the lesion was probably quite cellular or vascular. A microscopic diagnosis is never made by this method, but some intimation as to the degree of capillary vascularity, and cellularity, can usually be hazarded, and later this should be correlated with the clinical findings.

RECURRENT TUMORS

This radioactive isotope external localization test is particularly of value in the diagnosis of *early* tumor recurrences. Other neurosurgical diagnostic procedures are quite fallacious in this respect, for pneumograms always show distortions of the ventricular pattern which is the secondary result of the operative defect and due to gliosis and postoperative fibrosis. For the same reason, angiography will show abnormal vascular patterns postoperatively, and electro-encephalography will also show abnormal electrical patterns which are difficult to interpret from findings in cases of early tumor recurrences. Clinically, the difficulty may be even greater. For example, in the early differential diagnosis of postoperative focal epilepsy, it is difficult to decide whether the seizures are due to gliovascular changes secondary to surgery, or an early tumor recurrence.

This feature assumes vast importance in those benign tumors whose removal results in a prolonged survival time for the patient, for the more complete and the earlier the removal of a recurrent benign tumor, the better the eventual prognosis. Follow-up studies now take only 15 to 20 minutes, and their results have correlated extremely closely with the degree of completeness or incompleteness of removal of the tumor at surgery.

Importance in Bronchogenic Carcinoma: These tests have already proved to be

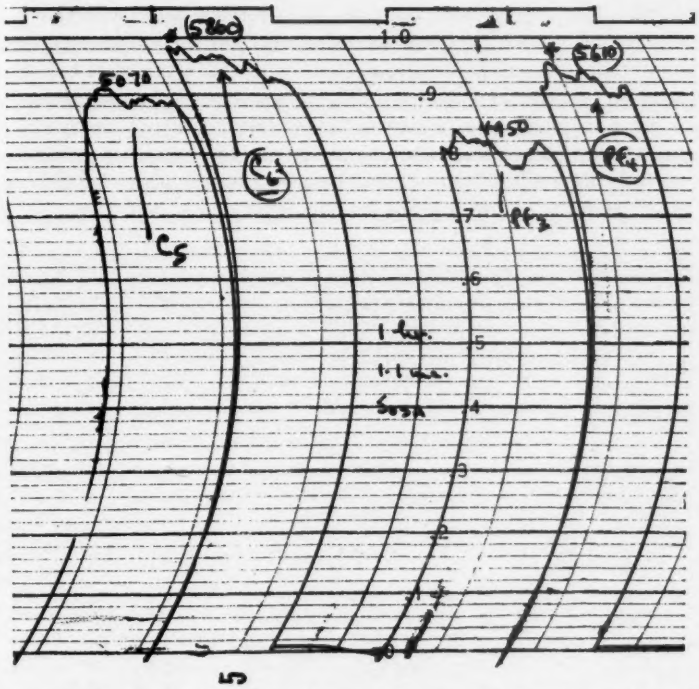

FIG. 3. Patient, A. S., had an extensive resection of a malignant glioma in the right frontal lobe about a year before this record was taken. He had three month follow-up radioisotope records which showed an increasing focus in the areas outlined in figure 4. This despite the fact that clinically the patient continued to improve and showed no further signs of his previous hemiparesis, and was able to return to full duty as a lieutenant colonel in the army reserves. By frequent follow-up studies like this, early tumor recurrences are detected before the patient shows clinical signs of the same. This partial record shows an 810 counts per minute difference favoring the C-6 position and a 660 count difference favoring the right prefrontal position.

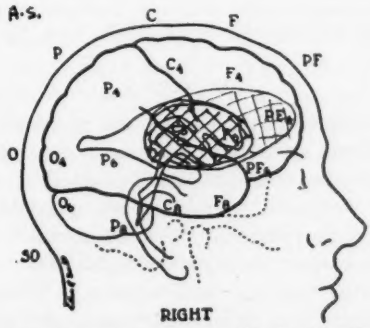

FIG. 4. This is the diagrammatic representation of the focal findings in the right prefrontal, inferior central, and superior temporal areas as manifested in figure 3. The focal accuracy of this lesion was later verified at reoperation.

of great value to services other than the neurosurgical and particularly to the thoracic surgeons, in their decisions to perform radical pneumonectomy or lobectomy for primary bronchogenic carcinoma. By scanning the skull following the administration of either radioactive diiodofluorescein or iodinated human serum albumin, we have been able to rule out metastatic lesions to the brain, which when present, would of course obviate the necessity of such extensive surgery. These metastatic cerebral lesions have usually been detected by this method much earlier than by any of our present clinical means of detection.

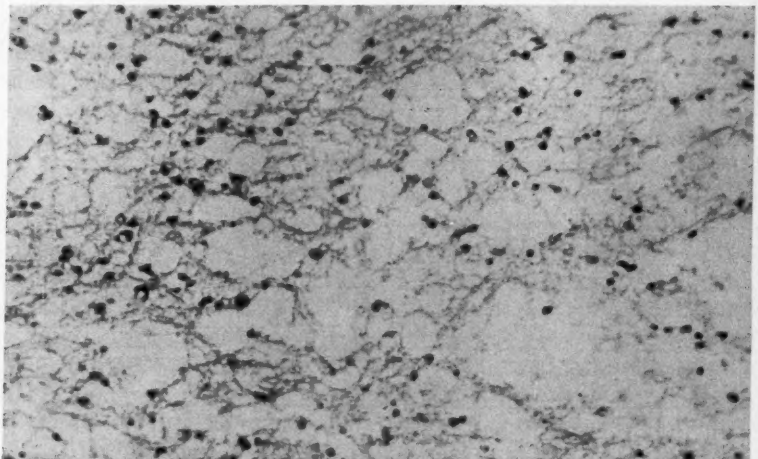

FIG. 5. In this patient, a very accurate focal localization was obtained by the use of the radioisotope technic, on the *opposite* side of the cerebrum. In actuality, this relatively acellular multi-microcystic astrocytoma with its scarcity of capillaries, was reading *lower* on the involved side instead of higher on the uninvolved side. This is one of the main limitations of the test, that is in the presence of highly cystic or necrotic or avascular lesions, where the uptake of radioisotope is actually lower than even on the normal side of the brain. This again proves that any good test such as this is an adjunct only, and must be correlated with the total clinical picture.

LIMITATIONS

With the use of such highly sensitive equipment as the scintillation counter, the need for a highly trained electronic biophysicist is essential. To obtain good results, the technic must be standardized and positioning, in particular, must be assiduously attained. The more normals obtained for the various supra and infra-tentorial and midline positions, the more accurate of course will be the interpretation and the various variations from normal.

This isotope localization test continues to prove to be a very valuable adjunct in neurosurgical problems, and, as in every other good test, is of even greater value when correlated with the clinical findings and the other neurosurgical diagnostic procedures. Again it was noticed in these more recent studies with newer

radioactive isotopes that the affinity of the isotope for tumor tissue is related to the cellularity and vascularity of the lesion with the more malignant ones showing the greater degree of concentration. Potential errors will occur in those relatively avascular tumors such as the oligodendrogliomas and the astrocytomas. Macrocystic and microcystic and centrally degenerative or necrotic lesions have at times yielded even lower than normal readings since only the active cellular and vascular tissue concentrated the radiodye (fig. 5).

False positives will result if the test is done immediately following major epileptic phenomena. In such instances repeat studies, if feasible, will indicate the presence or absence of progressive changes in permeability of the blood-brain barrier. A microscopic diagnosis of tumor or abscess or subdural hematoma cannot be made by this method; only some intimation as to the degree of capillary vascularity and cellularity is hazarded and later correlated with the clinical findings. The selective deposition of the radiodye or larger colloid particles within tumor tissue appears to be dependent mainly upon the state of the capillary endothelium, and these concentrations are directly proportional to the histopathological patterns of the blood vessels, particularly the terminal capillaries.

CONCLUSIONS

With the use of a highly sensitive scintillation counter and RIHSA, a dynamic approach has been used not only in brain tumor detection studies but also in studies following seizures, following cranial trauma, and following diagnostic studies such as pneumography and angiography. Since radioactive diiodofluorescein actively remained in the vicinity of the cerebrum for approximately ½ to 2½ hours following intravenous administration, very little opportunity for such a dynamic approach by the use of serial readings could be entertained with this dye. However, since RIHSA is not a foreign substance to the blood serum, it is not as rapidly excreted as a foreign vital dye and, during its recirculation throughout a period of 24 to 72 hours and more, it has a greater opportunity to exude through the damaged capillary endothelial walls or the damaged blood-brain barrier and therefore can be readily detected through its tagged radioactive iodine gamma rays.

The importance of instrumentation and technic has again been emphasized.

Some tumors will show a marked focal uptake on a 20 to 30-hour reading following one injection of RIHSA, whereas only a minimal uptake will be present on a six-hour reading; the opposite also occurs in other types of lesions, hence, the importance of serial studies. In a metastatic tumor, each of the nodules varies particularly in the time of uptake of the radioactive isotope, and this is correlated with the degree of vascularity and cellularity and necrosis.

The importance of these studies to detect early tumor recurrences has been emphasized, particularly in benign tumors.

These tests have proved of great value to the thoracic surgeons in their decisions to perform radical pneumonectomy or lobectomy for primary bronchogenic carcinoma. Metastatic cerebral lesions have usually been detected by this method much earlier than by any of our present clinical means of detection.

The limitations of the tests have been discussed. There are no contraindications.

It is a safe and harmless test of great focal accuracy, which when taken in conjunction with our other clinical means, has proved to be a very valuable diagnostic adjunct in neurosurgical problems in particular.

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THE SURGICAL TREATMENT OF MITRAL STENOSIS BY COMMISSUROTOMY: REPORT OF FIFTY CASES*

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About 50 years ago Brunton[4] and later Samways[15] suggested that mitral stenosis is in effect a mechanical problem and should therefore be amenable to surgical correction. Not until some 20 years later did Cutler and Levine[11] report the first actual clinical attempts at mitral valvulotomy. During the ensuing years these and a few other surgeons (Allen and Graham,[10] Pribram[10] and Souttar[17]) made a total of 10 such attempts, in only 2 of which did the patients survive the operation and only 1 of these 2 obtained a successful result. The latter patient was operated upon by Souttar to whom credit belongs for performing the first successful commissurotomy by digital dissection. This single successful case did not appear to justify the prohibitive operative mortality of 80 per cent in the entire group and further clinical trials of mitral surgery were not made for the next two decades.

Recently the inspiring work of Smithy,[16] Bailey,[1] Harken,[13] and Brock[3] has made the surgical relief of mitral stenosis feasible and has offered salvation to patients otherwise resigned to invalidism. Perhaps the most important single feature of the current technic of valvulotomy which accounts for the striking improvement in results is prevention of mitral regurgitation after valvulotomy by accurate control of the enlargement of the mitral orifice. In most of the earlier attempts valvulotomy was accomplished blindly, usually by introducing a valvulotome into the left ventricle in order to punch out more or less at random a piece of the stenotic valve. In instances in which this purpose was accomplished severe and frequently fatal mitral insufficiency was produced. Now it is recognized that valvulotomy must be done by division of the point of fusion of the valve leaflets. The anteromedial leaflet is vital, serving as a baffle to the left ventricular outflow tract (fig. 1) assisted to a lesser degree by the posterolateral leaflet in preventing reflux into the left atrium. In order to protect these leaflets and at the same time increase the size of the orifice, the valvular division is made at the point of fusion of the leaflets, known as the *commissures*. By this procedure maximum relief of the mitral stenosis is obtained and at the same time valvular action remains undisturbed or is actually improved.

This report deals with the first 50 consecutive patients who have undergone mitral commissurotomy on the surgical service of the Baylor University College of Medicine between March 1951 and October 1952. The patients who were selected for operation were considered to have mitral stenosis in a relatively *pure*

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form, although moderate degrees of mitral insufficiency did not preclude surgical intervention. Details of clinical evaluation of patients with indications and contraindications for operation will be reported elsewhere.[5] Cardiac catheterization was performed in the first 30 consecutive patients in this series[6] but in the last 20 patients it has been done only occasionally. These studies showed elevation of pulmonary arterial and pulmonary capillary pressures at rest and particularly with exercise. In most cases cardiac output during rest and exercise was below normal and in general reflected the degree of functional incapacity. Normally the cross sectional area of the valve as determined by the formula of Gorlin and

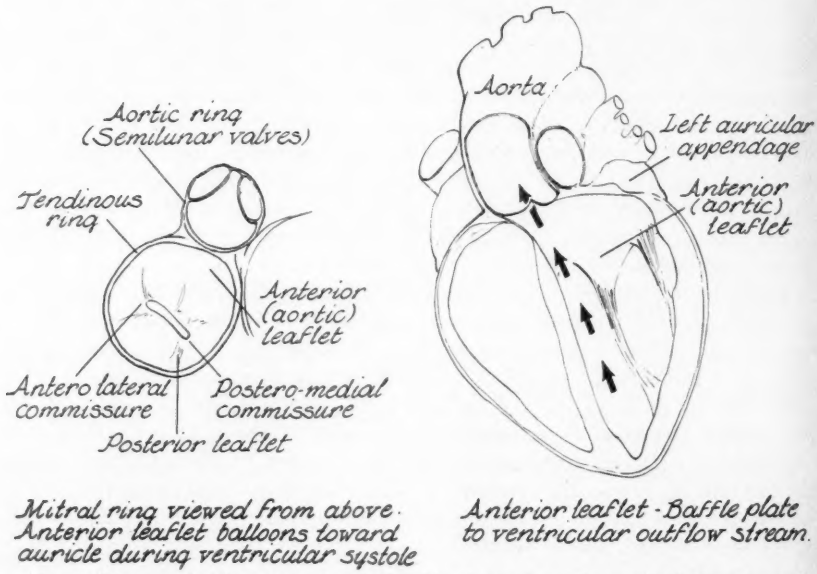

FIG. 1. Diagram showing anatomic relationship of anterior and posterior leaflets to aortic valve and to left ventricular outflow tract demonstrating importance of anterior leaflet as baffle plate which prevents regurgitation of blood into the left atrium during systole. "Commissurotomy" preserves vital valvular function without increasing mitral insufficiency.

Gorlin[12] is 4 to 6 sq. cm., but in almost all our patients the calculated valve area was less than 1.5 sq. cm. Moreover, there was a relatively close correlation between the calculated valve size and the size estimated by palpation at operation.

Patients were prepared for operation by digitalization, salt restricted diets and mercurial diuretics. One hour before operation quinidine sulfate (3 to 6 grains) was administered orally. Anesthesia was induced by use of either pentothal or nitrous oxide, and ether was substituted utilizing high concentrations of oxygen administered by an intratracheal tube. For the most part cardiac arrythmias other than extrasystoles were not serious during operation and only occasionally was quinidine lactate given parenterally or intravenously during anesthesia. Intra-

venous or topical administration of procaine hydrochloride and procaine amide were not employed in this series of cases.

The operative technic employed in these patients has been described in detail elsewhere.[9] Therefore only a brief description will be given. The patient lies supine on the operating table with the left shoulder slightly elevated and the left arm suspended from an overhead frame. A curved anterior submammary incision is made on the left, and the chest is entered through the fourth intercostal space after dividing the fourth costal cartilage. After insertion of a self retaining retractor, the left lung is partially collapsed and the pericardium is entered anterior and parallel to the phrenic nerve and vessels. The incision in the paricardium provides adequate exposure of the pulmonary artery and left auricular appendage. Pressures are measured in the pulmonary artery, left atrium, and aorta with a Sanborn manometer and Polyviso cardiette and simultaneous electrocardiograms are made. A purse-string suture of No. 0 black silk is placed around the base of the atrium to be employed for control of hemorrhage when necessary. A noncrushing clamp is placed across the base of the appendage and near its apex an incision is made sufficiently large to accommodate snugly the index finger. Then as the auricular clamp is removed slowly, the index finger is inserted into the cardiac chamber. Exploration of the atrium reveals whether or not mural thrombi are present, the elasticity and suppleness of the leaflets, the presence of calcification of the valve, and the degree of mitral regurgitation. The finger is introduced into the mitral orifice for no more than four or five heart beats so that the cardiac output is not impaired for a significant period. As the finger is withdrawn into the atrium, the operator checks again for a regurgitant jet of blood palpable during systole. Usually a carefully performed commissurotomy produces no mitral insufficiency. As the finger is withdrawn from the heart, the auricular clamp is reapplied simultaneously and with little or no blood loss. The auricular appendage is then amputated close to its base after the purse-string suture has been removed. The auricular opening is sutured with a double row of interrupted silk sutures and pressures are again measured in the pulmonary artery, left atrium, and aorta for comparison with tracings made before commissurotomy. The pericardium is sutured loosely to allow drainage of percardial fluid into the pleural cavity. An intercostal catheter is inserted into the pleural cavity for underwater drainage and the incision is closed in layers. Ordinarily the amount of blood lost does not necessitate a blood transfusion.

After operation digitalization and salt restriction are maintained. Hemorrhagic shock rarely occurs. In all patients with a sinus rhythm before operation quinidine sulfate (3 grains every four hours) is administered postoperatively to prevent the development of auricular fibrillation. In about 10 patients with sinus rhythm before operation fibrillation has occurred postoperatively and in all but one the rhythm was converted by quinidine in larger doses. In our opinion it is desirable to maintain a sinus rhythm whenever possible because of the greater cardiac output. In most instances an attempt is made to convert the rhythm to sinus in patients with chronic auricular fibrillation after they have recovered

from the operation. The usual period of postoperative hospitalization is eight days.

CLINICAL RESULTS

Since the first patient in this series of 50 patients was operated upon for mitral stenosis, there have been four deaths, three of which were operative fatalities inasmuch as they occurred during the first week after operation. The fourth occurred four months following the surgical procedure. In all 47 patients who survived operation an attempt has been made to estimate the degree of improvement, based on relief of symptoms, functional improvement, and, when possible, information obtained by cardiac catheterization. Results were considered good in 35 (74 per cent) of the survivors, fair in 9 patients (19 per cent) and poor in 3 (7 per cent). In many of those whose result was classified as good, not only was functional activity completely restored but cardiac murmurs were almost totally eliminated. In others the functional improvement was good, but there was less striking alteration of the cardiac murmurs.

Deaths: The four deaths in this series occurred in severely incapacitated functional Class IV patients, 3 of whom were in the older age group, their respective ages being 49, 51 and 53 years. Moreover, 4 had auricular fibrillation of many years' duration, and significantly 3 of these died of peripheral embolism. The first fatality was caused by an aortic *saddle* embolism occurring immediately after operation in a man 51 years old who had previously had iliac emboli. Cerebral embolism caused death on the third postoperative day in a woman 49 years old whose left atrium on exploration was completely lined by thrombosis. In the third fatality death occurred four months after operation from aortic *saddle* embolus, although embolectomy had been performed eight hours earlier; this patient showed functional improvement prior to the terminal event. The fourth patient to die after operation was a housewife 31 years old who had advanced left and right ventricular enlargement and intractable cardiac decompensation before operation. Exploration of the valve revealed severe mitral regurgitation, so commissural dissection was not done. Death ensued five days later presumably from progressive heart failure.

Severity of cardiac condition: The patients in this series were grouped prior to operation according to the classification for functional capacity proposed by the New York Heart Association.

As shown in Table I more than 40 per cent of the patients in this series were considered to be Class IV, and 90 per cent were in either Class III or IV. Many of the patients were severely disabled and 5 had been totally bedfast for more than three months. The percentage of good to fair results was higher in Class III than it was in Class IV, although good results were obtained in about 60 per cent of the patients in Class IV. This high percentage of good results in Class IV patients would appear to offset the fact that all four deaths occurred in this group. Operation thus seems to be justified in these patients who are otherwise destined to chronic invalidism or premature death.

Age: The ages of the patients were fairly equally divided between those more

than 40 years of age (23 patients) and those who were less than 40 (27 patients). Sixteen patients were less than 30 years of age, the youngest being 19 years. In all patients less than 25 years of age the possibility of reactivation of the rheumatic process by operation deserves consideration. Thus, all of our younger patients were observed carefully for varying periods before operation. Three patients in the younger group have had transient symptoms following operation strongly suggestive of a recrudescence of rheumatic fever. In general, however, the most satisfactory results were obtained in patients between the ages of 25 and 35 years. In patients more than 40 years of age good results were obtained in 10 (44 per cent) and there were three (13 per cent) deaths. In patients less than 40 years of age good results were obtained in 23 (85 per cent) and 1 patient (3.7 per cent) died. Although the fatality rate in the older patients was higher than in the younger group, the percentage of good results in the patients above 40 years of age justifies operation in these patients. The oldest patient in this series was 53 years but operation is now being considered in a man 58 years old.

TABLE I

Table shows functional classification (New York Heart Association) in 50 patients undergoing mitral commissurotomy. Class I patients have least incapacity and Class IV the greatest functional impairment.

Functional Classification	No. of Cases	Per Cent of Cases
I	0	0
II	5	10
III	24	48
IV	21	42
	50	100

Previous Embolism: Peripheral embolism occurred before operation in 11 patients and in 4 of these there were multiple emboli. Seven patients had cerebral emboli producing neurological sequela such as hemiparesis and dysphasia. In others the emboli lodged in the vessels of the extremities or viscera (spleen, kidney, intestine). Several patients were suspected of having pulmonary infarctions before operation but in all of these the evidence was equivocal. Eight of the patients with previous peripheral emboli were fibrillating at the time of operation. In 4 of the 11 patients thrombi were demonstrated in the left atrium at operation but in only 1 of these did embolism occur after operation and in this case it was fatal. Moreover, this latter case is the only 1 in the group of patients with peripheral embolism before operation to have an embolus subsequent to valvulotomy. Thus it appears that peripheral embolism in the presence of mitral stenosis is actually an indication for valvulotomy and offers lasting protection against embolization.

Auricular Fibrillation: Before operation 24 patients had auricular fibrillation and 26 patients had sinus rhythm. In those with fibrillation good results were obtained in 15 (62 per cent), whereas in the patients with sinus rhythm 18 (69

per cent) obtained good results. This would suggest that auricular fibrillation does not significantly diminish the possibility of obtaining a good functional result in those patients who survive operation. On the other hand, all 4 patients who died had fibrillation and in three instances death resulted from embolism. These results would indicate that while auricular fibrillation is not a contraindication to valvulotomy, it does apparently increase the operative risk and slightly diminish the possibility of a good functional result. Of real importance in auricular fibrillation is the frequency of mural thrombosis in the auricle. In the 16 patients with fibrillation mural thrombi were demonstrated in the left atrium or auricular appendage in seven instances (29 per cent). In 3 of these embolism was discovered soon after operation. In 1 the embolus involved pulmonary vessels indicating that there was right atrial thrombosis as well as left. In the patients who had postoperative embolism, 1 had no thrombus in the atrium or appendage discovered at operation, but this patient died four months later, and it is possible that the thrombus which produced the fatal embolus developed after operation. Measures taken at operation to reduce the danger of embolism have been employed in all patients with auricular fibrillation and mural thrombosis. In all patients the valve has been approached through the auricular appendage whether or not it is suspected of containing thrombi. Utilizing the left superior pulmonary vein for this purpose is not recommended because uncontrollable hemorrhage has been reported in such attempts.

Before entering the auricular appendage an attempt is made to cleanse the atrium and appendage of any contained thrombi by releasing the auricular clamp to allow a gush of blood to wash out any loosely attached thrombi. In 3 patients the left atrium was completely lined by thrombi in varying stages of organization. In these cases the thrombus was gently dissected away from the endocardium before valvulotomy was accomplished. Two patients recovered uneventfully and the third died of a cerebral embolus five days later. Although it seems desirable during intracardiac manipulation to have the anesthetist compress the carotid arteries to prevent cerebral embolization, the fact that in the single case of postoperative cerebral embolus this technic was employed indicates that it is not entirely reliable. A technic suggested by Bailey[2] for temporary complete occlusion of the carotid circulation within the thorax has been employed recently and probably can be recommended as a more reliable measure to prevent cerebral embolism during commissurotomy. Neither of these measures, however, precludes the possibility of emboli lodging at the aortic bifurcation and 2 of our patients died from this cause. Anticoagulants have been employed after surgery in some of the patients but not in a sufficient number from which to draw conclusions.

Valvular Calcification: Calcification of the mitral valve was present in 24 patients (48 per cent) in this series. In some instances calcification was extensive and involved the valve leaflets as well as the commissures and in a few, it occurred only at the commissures, usually the anterolateral one. Occasionally, the calcium deposition was exuberant, possibly representing calcified vegetations. When only one commissure was calcified, it was usually possible to obtain a satisfactory functional result by splitting the other commissure. In some instances, when a split is made through a calcified commissure, mild mitral insuffi-

ciency may be produced. In the presence of calcification the commissural incision should be made gradually in order to control the degree of mitral insufficiency which may follow a jagged split extending into the valve ring. In no instance did embolization of a calcified fragment occur and in no instance did bacterial endocarditis commence on the irregular margin of the valve. Of the 24 patients in whom calcification of the valve was discovered at operation, good results were obtained in 13 patients (54 per cent), fair results in 7 patients, and 4 patients died. The more extensively calcified valves may be demonstrated by roentgenography or fluoroscopy, but from our experience this does not contraindicate exploration.

Associated Valvular Lesions: In none of our patients was a significant degree of aortic stenosis or aortic insufficiency present. Aortic insufficiency was strongly suspected in 1 patient because of slight enlargement of the left ventricle and the presence of a diastolic murmur to the left of the sternum. The fact that the murmur disappeared after commissurotomy indicated that this murmur had been the Graham-Steel murmur of functional pulmonic insufficiency due to the accompanying pulmonary hypertension. Increasing experience indicates that the Graham-Steel murmur is a frequent finding in pure mitral stenosis and is often mistaken for aortic insufficiency. In each case in which a satisfactory surgical result was obtained the Graham-Steel murmur disappeared. Before operation, none of our patients demonstrated the presence of an associated tricuspid lesion or a pulmonary valvular lesion. In 12 patients there was associated mitral insufficiency of varying degree. The finding of mitral insufficiency was proved in all cases at operation by palpation of the regurgitant stream during systole. Two patients in this series were demonstrated at exploration to have predominantly mitral insufficiency. Both patients were submitted for operation with severe cardiac decompensation and cardiac enlargement in the hope that mitral stenosis was partially responsible for the disability; 1 patient was improved by commissurotomy and the other died.

In general, the finding of a Grade I or II mitral systolic murmur with mild left ventricular enlargement does not preclude surgical treatment in patients in whom mitral stenosis is the predominant lesion. A carefully performed mitral commissurotomy seldom increases the degree of mitral insufficiency. In 2 patients, however, it was thought that mitral regurgitation was increased by the commissurotomy, but in both instances the relief of mitral stenosis produced the desired functional improvement. Commissural dissection should be performed with extreme care so that valvular action is restored and the stenosis relieved without producing a totally incompetent valve. Mild mitral insufficiency frequently accompanies mitral stenosis, but in properly selected cases even here commissurotomy will produce striking functional improvement.

Pregnancy and Mitral Stenosis: Two patients in this series were pregnant at the initial examination.[8] One was a 28 year old primigravida in the fourth month of pregnancy. Several years previously she had two attacks of congestive failure and during pregnancy she had noticed progressive disability. Commissurotomy produced an excellent functional result and five months later she delivered uneventfully a 7 pound normal female infant.

The other patient was a 24 year old primigravida in the eighth month of preg-

nancy. Prior to pregnancy she had had relatively little disability, but since the onset of pregnancy she had had two attacks of severe pulmonary edema notwithstanding a rigid cardiac regimen. Operation was performed during the thirty-sixth week of pregnancy and 62 hours later she delivered a 5 pound 10 ounce male infant. Mother and son were discharged from the hospital 5 days after delivery in good condition.

These cases illustrate the feasibility of commissurotomy during pregnancy. If commissurotomy is anticipated under such circumstances, the optimum time for operation is before the fifth month of pregnancy. After the first trimester the cardiac output increases rapidly, reaching a maximum during the thirty-sixth week and then cardiac output declines until the time of delivery. Ordinarily delivery is well tolerated but during the first 72 hours after delivery the heart again is under strain and cardiac failure may ensue. Further experience is necessary before other specific recommendations can be made in regard to cardiac surgery during pregnancy.

COMMENT

In all operations the pressures in the left auricle, pulmonary artery and a systemic artery have been measured. Indication of a good immediate response to commissurotomy is the immediate fall in mean pulmonary artery pressure and also in the left atrial pressure of 15 or 20 mm. Hg. In several patients whose mean pulmonary arterial pressure was exceedingly high (90 to 110 mm. Hg) the pressure did not fall immediately after commissurotomy notwithstanding a significant drop in left atrial pressure. This indicates that in some patients with mitral stenosis the vascular changes in the pulmonary vessels may delay the restoration of normal pulmonary pressure after operation. These vascular changes have been described in detail elsewhere[14] and in all of our patients such histologic changes have been investigated by lung biopsy specimens and will form the basis of a subsequent report.

Recurrence of mitral stenosis after commissurotomy has not taken place in any of our patients and must be rare probably because the rheumatic infection is quiescent in patients selected for operation. Other factors too are undoubtedly responsible for this gratifying observation, but we have thought it desirable to study histologically the amputated auricular appendage from all patients. Although endocardial thickening and subendocardial infiltration with round cells has been noted in most specimens, Aschoff nodules were described in only a few specimens and other histologic findings of acute rheumatic carditis have not been demonstrated.

SUMMARY

In a series of 50 patients who have undergone valvulotomy for mitral stenosis there have been four deaths, three of which were operative deaths. Peripheral embolism caused death in 3 and progressive cardiac decompensation in the fourth.

The rationale and technic of commissurotomy is outlined briefly.

Forty per cent of the patients were Class IV cardiacs and 90 per cent either Class III or IV.

Optimum age for operation is between 20 and 40 years. Peripheral embolism occurred in 11 patients before operation and in only 1 of these has embolization occurred subsequent to valvulotomy.

Auricular fibrillation was present in 24 patients before operation. Fifteen patients in this group obtained good results and there were 3 deaths.

Commissurotomy during pregnancy was successful in 2 patients.

A relatively small degree of mitral insufficiency does not contraindicate commissurotomy. Mitral insufficiency was increased after commissurotomy in 2 patients although both were functionally improved. Recurrence of mitral stenosis after commissurotomy has not occurred.

Addendum: Since this report was submitted 13 more patients have undergone commissurotomy without an operative death. In this group there were two patients in the advanced age group, (52 and 58 years respectively) both of whom obtained excellent functional results.

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OBSERVATIONS ON PANCREATIC JUICE IN A CASE OF EXTERNAL PANCREATIC FISTULA IN MAN

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Whereas in the past most of the literature on pancreatic fistula has dealt with surgical technics in its repair, there has been in the last decade an increasing number of articles concerning physiologic observations in cases of external pancreatic fistula.[2, 3, 8, 12, 13, 14, 18, 21]

External pancreatic fistula may occur as the result of direct trauma to the pancreas,[8, 21] isolated nonpenetrating injuries of the pancreas,[7, 21] drainage of pancreatic cysts,[9] injury to the pancreatic duct in upper abdominal operations,[11, 13] and in cases of intubation of Wirsung's duct following transduodenal excisions of ampullary tumors,[17] the latter type constituting a total or complete external pancreatic fistula. Garis and Merkel[5] reported a case of complete pancreato-biliary fistula following cholecystectomy which developed due to obstruction of the duct of Wirsung by an unrecognized ampullary carcinoma, and at autopsy no accessory pancreatic duct could be found.

Recently an opportunity was presented to study a case of external pancreatic fistula following drainage of a pancreatic cyst which developed following an isolated nonpenetrating injury of the pancreas.

CASE REPORT

J. L., a healthy 27 year old man was seen on April 12, 1952, a short time after being in an automobile accident in which his lower chest and upper abdomen struck the steering wheel. Because of increasing abdominal findings, exploratory laparotomy was performed approximately 36 hours after injury. There was free blood in the abdomen and in the lesser peritoneal sac. Fat necrosis of the gastrohepatic and gastrocolic ligaments was noted. The head of the pancreas was enlarged and firm. The pancreas itself was not visualized.

On the fourth postoperative day the patient began to complain of persistant pain in the left upper abdominal quadrant and it was possible to outline a large globular mass in the left upper abdomen and epigastrium. Two days later laparotomy revealed a large pseudocyst of the pancreas (lesser peritoneal sac) from which was removed 2050 cc. of straw-colored fluid. Marsupilization of the pancreatic cyst was performed. Postoperatively the wound drained clear fluid and on the sixth postoperative day observations were begun on the pancreatic fluid drainage from the fistula. The patient was discharged from the hospital on the eightieth hospital day with only very small amounts of fluid draining from the fistula. A small rubber catheter had been inserted to keep the fistula open.

The patient was re-admitted on July 1, 1952, with pain in the left upper abdominal quadrant, the fistula having closed 24 hours previously and the catheter having fallen out 72 hours previously. Four days later incision and drainage was carried out, removing approximately 150 cc. of clear serous fluid. The patient was discharged on July 22, 1952, and the fistula was completely healed two weeks later.

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The patient ate the regular hospital diet and drank fluids as he desired. Inasmuch as there were no gross alterations in his digestive physiology it is assumed that the external pancreatic fistula was partial in nature. None of the collected pancreatic juice was returned to the patient. Duodenal juices were not analyzed for pancreatic enzymes. On the days that the pancreatic volume response to various drugs was carried out, fluids from midnight on as well as breakfast were withheld. The tests were usually carried out at 7 a.m. and the volume response noted for the hour following administration of the drug. At the conclusion of the experiment the patient was allowed to take fluids and the meals were resumed at noon.

The pancreatic juice was collected from a small mushroom catheter that had been placed inside the cyst during the second surgical procedure. The fluid was allowed to drip out of the tube into small sterile glass bottles, collections for the most part were made at hourly intervals. Variations in the length of the collecting periods were noted and taken into account in calculating the hourly volumes. Specimens for sodium, potassium and magnesium determinations were kept refrigerated until the determinations were begun. Inasmuch as chloride, bicarbonate, amylase and tryptic activity determinations were not done the day the specimens were collected, the specimens were frozen until the determinations were begun.

It was obvious during the initial volume response to a test drug that a slight change from the supine position of the patient would bring forth fluid that had collected in the fistula and would greatly increase the volume of secretion. Accordingly the patient was kept flat in bed for one hour prior to beginning the test and until the test was completed. McCaughan et al[11] experienced similar difficulty in the collection of samples. Otherwise the patient was ambulatory as he desired. This must be kept in mind in evaluating the results with regard to hourly volumes of secretions.

VOLUME STUDIES

24 Hour Volumes. Twenty-six 24 hour collections were made of the pancreatic secretions from the external pancreatic fistula, collecting periods running from 7 a.m. one day to 7 a.m. the next day. With a daily tendency towards decreasing output, the largest 24 hour volume obtained was 862 cc. on the first day of the study and the smallest volume obtained was 197 cc. on the twenty-second day of the study (fig. 1).

The total amount of pancreatic fluid collected over the 26½ day period was 11,665 cc.

12 Hour Volumes (day and night). Fifty-three consecutive 12 hour collections were made. The 12 hour collecting periods were divided into day volumes and night volumes, running from 7 a.m. to 7 p.m. and 7 p.m. to 7 a.m. respectively. A total of 27 night volumes and 26 day volumes were obtained.

The largest day volume was 576 cc. on the first day and the smallest day volume was 146 cc. on the twenty-third day. The largest night volume was 286 cc. on the first day when the 24 hour volume studies were begun but 351 cc. were

obtained the night prior to beginning the 24 hour volume studies. The smallest night volume was 47 cc. on the twenty-second day. The ratio of day volume to night volume for the entire 26 day period was 66:34. The greatest variation of day volume to night volume was 76:24 on the twenty-second day and the least variation was 50:50 on the twenty-fifth day (fig. 1).

Hourly Volumes. Collections of pancreatic juice at consecutive hourly intervals were obtained for 22½ days, affording a maximum total of 540 observations on hourly volumes. Each hourly volume was then expressed in terms of percent of the total 24 hour volume for the day (fig. 2).

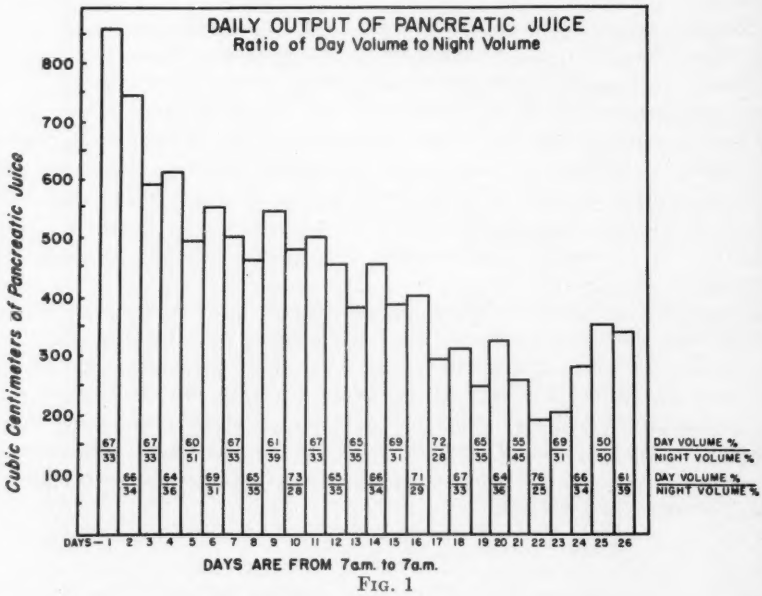

FIG. 1

There is a discrepancy in the total number of hourly volumes that are recorded, 476, and the possible maximum number, 540. There were times when the collecting periods ran considerably over the hour, sometimes becoming two hour specimens. The results of such volume collections were discarded, not affecting the remainder of the hourly observations of that particular period.

Certain conclusions may be drawn from the scattergraph on hourly volumes (fig. 2). First, the largest volumes of pancreatic secretion are noted following meals. In this patient it is possible that the largest volumes were obtained about midday inasmuch as that particular meal, 11 to 11:30 a.m., in our hospital is the largest meal of the day. A decrease in the volume secretion was noted in the afternoon. The volume increased in the evening after supper, 4:30 to 5 p.m. Following the evening meal the volume again decreased, reaching its lowest rates of secretion in the early morning, 1 to 6 a.m. The increase in rate of secretion fol-

lowing breakfast, 7:30 to 8 a.m., with subsequent decrease prior to the noon meal is not so clearly demonstrated because frequently breakfast was withheld and then was given at 9 or 9:30 a.m. following the experiments, and occasionally the patient was not given food until the noon meal.

Second, pancreatic secretion is continuous. This has been noted and discussed by others.[9, 10, 11, 13, 21]

Third, although pancreatic secretion is continuous, its volume of secretion from one hour to the next, and from one day to the next for the corresponding hour is quite variable, even though the patient is in the fasting state. It would appear then that to evaluate the response of pancreatic secretion to drugs by compari-

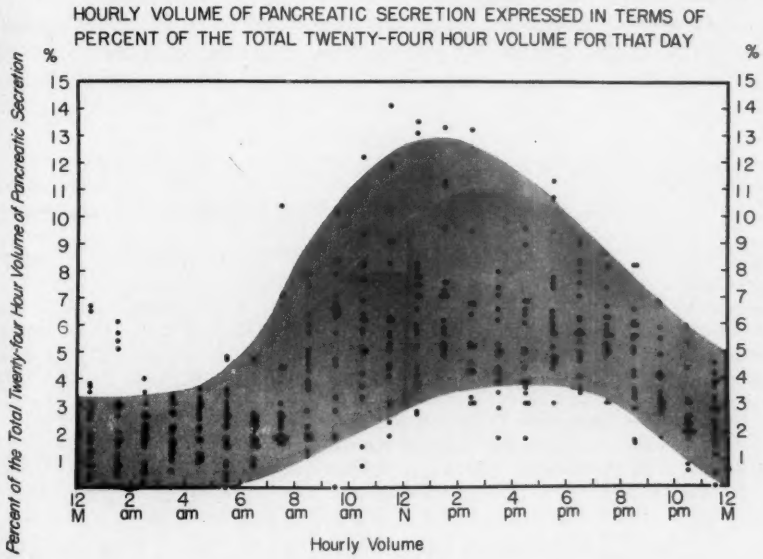

FIG. 2

son of a one hour volume secretion as a control with a one hour volume secretion following administration of a drug assumes a constancy of secretion which is not supported by the facts.

Specific Gravity. Recordings of specific gravity of pancreatic juice were made on 22 day (12 hour) specimens with a range of 1.003 to 1.007, the latter figure noted but once. Specific gravity on each of 23 night (12 hour) specimens were noted with a range of 1.003 to 1.006. The average specific gravity of the day specimens was 1.0047 and the average of the night specimens was 1.0046.

DATA ON VARIOUS CONSTITUENTS OF PANCREATIC JUICE AND THEIR PLASMA COMPONENTS

Data on 46 consecutive 12 hour specimens of pancreatic juice regarding sodium, potassium, chloride, magnesium, bicarbonate and amylase concentrations

are recorded (table 1). Tryptic activity was determined on seven of the specimens. Sodium and potassium concentrations in pancreatic juice and serum were determined by the method of Weichselbaum and Varney.[20] Magnesium concentrations in pancreatic juice and serum were determined by the method of Garner, using titan yellow.[6] The mercurimetric method for the determination of chlorides in biological fluids as described by Schales and Schales was utilized.[16] Tryptic activity was determined by the method described by Philipsborn et al, tryptic activity being measured by the amount of nitrogen liberated from a casein substrate.[15] The method of Folin and Wu was used for the nonprotein nitrogen determinations,[4] and amylase determinations were done according to the method by Wohlgemuth described in Bray.[1]

Sodium and postassium concentrations were found to be relatively constant in the day and night specimens of pancreatic juice, sodium being 144.5 and 143.7 meq/l respectively, and potassium being 4.5 and 4.6 meq/l respectively. Magnesium concentrations were usually higher in the night specimens, levels being 0.52 and 0.57 meq/l for the day and night specimens respectively.

TABLE 1

Values of various constituents of pancreatic juice (milliequivalents per liter)

	Average*	Range*	Average Day†	Average Night‡	Range Day†	Range Night‡
Sodium	144·1	140.1 –147.5	144·5	143.7	140·1 –147·5	140.1 –147.5
Potassium	4·54	3·8 – 5.2	4·5	4.6	3·8 – 5.2	4·1 – 5·2
Magnesium	0·53	0.28 – 0.78	0.52	0.57	0·28 – 0.63	0·43 – 0.78
Chlorides	85·5	60.0 –105.0	81·9	89.2	60.0 – 97.0	74.0 –101·0
Bicarbonate	59.5	43.0 – 78.0	63.1	55.8	49.5 – 78.0	43.0 – 66.0
Amylase§	3.855	1.375– 7.520	3.579	4.131	1·850– 6.125	1·375– 7.520

* Results of 46 consecutive 12 hour specimens.
† Results of 23 consecutive day (7 a.m.–7 p.m.) specimens.
‡ Results of 23 consecutive night (7 p.m.–7 a.m.) specimens.
§ Amylase values expressed in grams per cent.

Chloride concentrations were higher as a rule in the night specimens, 81.9 and 89.2 meq/l for the day and night specimens respectively while the reverse was true of the bicarbonate concentrations, 63.1 for the day and 55.8 meq/l for the night specimens.

Amylase concentrations in pancreatic juice were usually higher in the night specimens, levels being 3.579 and 4.134 grams per cent for the respective day and night specimens.

Tryptic activity expressed in grams per cent of nitrogen liberated varied from 0.18 to 0.95 and averaged 0.49 on seven observations.

Invariably higher concentrations of sodium, potassium, and bicarbonate occurred in pancreatic juice than in plasma, whereas chloride and magnesium concentrations were always higher in plasma than in pancreatic juice (table 2).

Volume Response of Pancreatic Secretion to Drugs. Observations on the volume response of pancreatic secretion to splanchnic block, banthine, secretin and

whiskey were performed. It has been shown (fig. 2) that the volume of pancreatic secretion from one hour to the next is quite variable and therefore the comparison of a one hour volume secretion as a control with a one hour volume secretion following administration of a drug is an inaccurate method of evaluating volume response to a drug. In an effort to minimize this variation it was decided as the

TABLE 2

Concentrations of similar constituents in plasma and pancreatic juice (milliequivalents per liter)

	Plasma	Pancreatic Juice
Sodium	132·9	144.1
Potassium	3·9	4.5
Magnesium	2.01	0·53
Bicarbonate	27·2	59.5
Chloride	100.0	85·5

Plasma determinations of sodium, potassium, and magnesium based on 11 observations, bicarbonate on 10 observations, and chlorides on 14 observations. Results of determinations on pancreatic juice based on 46 consecutive 12 hour specimens.

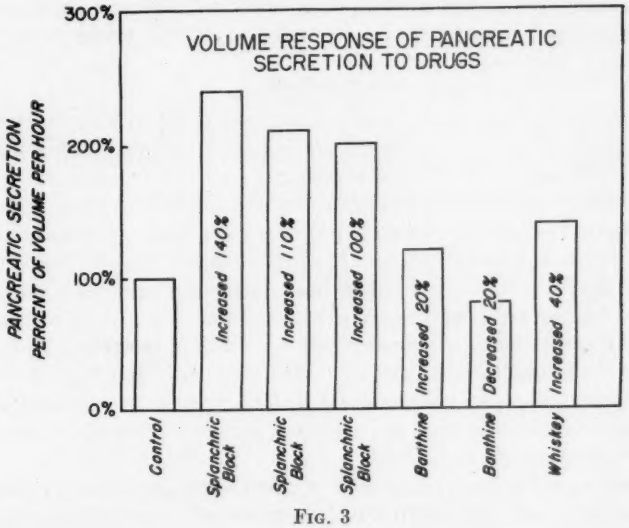

FIG. 3

tests were performed at 7 a.m. to use as a control an average of all the hourly volumes between 6 to 7 a.m., expressed as per cent of 24 hour secretion, some 21 observations in all. In retrospect it would have allowed for greater accuracy to have obtained some fasting volume controls from 7 to 8 a.m., the hour the tests were usually performed.

Splanchnic block was performed three times, injecting 10 cc. of 1 per cent procaine hydrochloride bilaterally at the level of the twelfth thoracic vertebra,

and the volume responses noted. The hourly volume of pancreatic secretion was increased by 140 per cent, 110 per cent and 100 per cent (fig. 3).

Banthine, in an intramuscular dose of 100 mg, in two tests reduced the volume by 20 per cent on one test and increased the volume by 20 per cent on the second test (fig. 3).

Whiskey, 60 cc. given orally, produced an increase in hourly volume by 40 per cent the one time it was used (fig. 3).

Secretin produced a marked increase of 200 to 300 per cent in hourly volume which was maintained for four hours, but a rather immediate secretin reaction occurred. The initial skin test performed by administering 0.1 cc. of secretin subcutaneously was interpreted as negative at the end of 15 minutes. It was originally intended to give the patient 80 units of secretin intravenously but half of the dose was inadvertently lost during mixing. Two minutes after intravenous administration of 40 units of secretin the patient began to complain of griping abdominal pain. This was soon followed by generalized pruritus, increased lacrimation, injection of the conjunctivae, diaphoresis and apprehension. The patient became short of breath six minutes after receiving the secretin and asthmatic rales were noted in both lung fields. Two injections of adrenalin were given 20 minutes apart with only temporary cessation of the pruritus following the initial injection. The reaction appeared to have subsided 25 minutes after the last injection of adrenalin and 55 minutes after the secretin had been given.

SUMMARY

1. Observations on a case of external pancreatic fistula in man revealed that approximately two-thirds of the pancreatic juice is secreted during the day and approximately one-third during the night.

2. Pancreatic secretion is continuous, but its volume of secretion from one hour to the next and from one day to the next for the corresponding hour is quite variable. It would appear then that to evaluate the response of pancreatic secretion to drugs by comparison of a one hour volume secretion as a control with a one hour volume secretion following administration of a drug assumes a constancy of secretin which is not supported by the data presented. In an effort to minimize the variation in hourly volume of pancreatic secretion, an average of multiple observations on volume secretion for a given hour expressed as per cent of 24 hour secretion was used as the control in determining the volume response of pancreatic secretion to drugs.

3. Secretin, splanchnic block, and whiskey each produced increases in the volume of pancreatic secretion. Banthine produced a moderate decrease in one test and an increase in another.

4. Specific gravity of pancreatic juice was the same during the day and night. Sodium and potassium concentrations were found to be relatively constant in the day and night specimens of pancreatic juice. Chloride and amylase concentrations in pancreatic juice were usually higher in the night specimens while the reverse was true of the bicarbonate concentrations. Magnesium concentrations were slightly higher in the night specimens of pancreatic juice.

5. A rather severe reaction to intravenous secretin is described.

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ACUTE GASTRODUODENAL PERFORATION; AN ANALYSIS OF FORTY-FOUR CASES TREATED BY IMMEDIATE GASTRECTOMY

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Immediate partial gastric resection for acute gastroduodenal perforation has been employed and advocated in European clinics for many years.[11, 12, 14, 18, 20, 24, 25] In 1902 Keetley[19] in England performed a limited gastric resection with gastroduodenostomy (Billroth I) in a patient with an acute gastric perforation. As early as 1919, at a time when gastric resection for chronic peptic ulceration was just beginning to find popularity, von Haberer[15] advocated gastrectomy for the acutely perforated ulcer. More recent reports from the continent dealing with large series of cases with perforation have indicated that gastric resection need not be more hazardous than simple closure under such circumstances. Thus, Judine[17] in Russia reported in 1939 a personal series of 937 cases with a mortality of 8.9 per cent. More recently Banzet[2] in France reported a large series of cases with an even lower mortality, and Carayannopoulos[6] in Greece reported 56 cases with a mortality rate of 3.57 per cent.

In this country a more conservative attitude toward immediate gastrectomy for acute gastroduodenal perforation was maintained notwithstanding these favorable reports. This stand was based on the belief that the surgeon's responsibility in an acute abdominal episode was solely to save life.[13] Simple closure was thought to be associated with less postoperative morbidity and mortality. Moreover, the opinion was widely held that recurrence of ulcer symptoms after perforation was infrequent, and that further surgery was usually not required.[8] Recent studies, however, suggest that this attitude was not well founded. Long term follow-up observations on patients after acute peptic gastroduodenal perforation indicate that between 75 and 80 per cent of these cases have further symptoms and that about 35 per cent require subsequent surgical treatment.[29] Moore, et al,[22] noted in patients with acute perforation followed for a minimum of two years that the results were unsatisfactory in 45.3 per cent of the cases, while in those patients with relapse of symptoms after perforation the results were unsatisfactory in 85.3 per cent of the cases. Evidence for a more aggressive attitude in such cases is obtained from Luer[21] who stated that over 10 per cent of cases of peptic ulcer with perforation treated by simple closure reperforate within a five year period. Instances of reperforation in the early period following closure are not infrequent, and 1 case in the present series had a second perforation two months after simple closure and was treated successfully by immediate gastrectomy. An increasing number of investigators[29] are being led to conclude

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that perforation of a peptic ulcer is good evidence of intractability or virulence of the lesion requiring more definitive surgical therapy such as gastric resection.

The risk of major gastric surgery has been markedly reduced in recent years. This is explained by the widespread use of more effective antimicrobial therapy; by blood and electrolyte replacement; by improvements in anesthesia; and by perfection of surgical skill. The mortality for gastric resection in chronic peptic ulceration has been reduced to less than 3 per cent,[1, 2, 27, 29] in most clinics, and furthermore, gastric resection has yielded a high proportion of good results in the more complicated cases. For example, De Bakey[8] in 1940 reported good results in 90 per cent of cases undergoing gastric resection for perforated ulcer. More recently, Rauch[26], in an analysis of 893 cases of partial gastrectomy reported 89.6 per cent good results in long term follow-ups. In view of these considerations, it appears that the surgeon's responsibility in a case of acute gastroduodenal perforation extends beyond expediency of simple closure and should include curative gastric resection in selected cases.[3] This clinical study was undertaken in order to evaluate more closely immediate partial gastric resection in acute gastroduodenal perforation in an effort to define its indications and limitations.

CLINICAL MATERIAL

Since September 1951, 44 patients on the surgical service of Baylor University College of Medicine, have undergone gastric resection for acute gastroduodenal perforation. No strict criteria were established in regard to age, previous ulcer symptoms, or duration of perforation to guide the selection of cases during the course of this study. Rather the selection of cases for resection was determined by the judgment of the resident or staff surgeon in attendance. A majority of the cases in which resection was done demonstrated the typical clinical picture of acute gastroduodenal perforation as manifested by sudden abdominal pain, board-like abdominal rigidity, loss of percussable hepatic dullness, absent peristaltic sounds, and roentgenographic evidence of pneumoperitoneum. The diagnosis was usually established within a few minutes after arrival at the hospital. In all cases nasogastric suction was begun immediately and the contents of the stomach thoroughly aspirated usually with almost instant relief of pain. The patient was then given a thorough examination and in most instances plans were made to proceed with a gastric resection. Most of the patients were thus submitted to immediate gastrectomy shortly after their arrival at the hospital. Blood counts and urinalyses were done routinely and blood was matched for possible transfusion. The operating room was notified soon after the patient arrived to avoid unnecessary delay.

A general anesthetic with endotracheal intubation was used in most of the cases. Abdominal exploration was done most frequently through a midline incision from the xyphoid to the umbilicus. The midline incision offered adequate exposure and permitted rapid entry into the abdomen. Usually the perforation was found covered by fibrinous exudate with the opening partially or completely sealed by the adjacent viscera. In gastric perforations there was little difficulty in freeing of adhesions which could usually be done by finger dissection. Likewise

in duodenal perforation, there was frequently no fixation of the duodenum to the head of the pancreas and the dissection necessary to mobilize the duodenum was easy. The amount of edema and early inflammatory change in the wall of the duodenum actually seemed to facilitate dissection in this region in a manner similar to that found in acute hydrops of the gallbladder. There is experimental evidence to show that the amount of inflammatory edema in these cases does not interfere with healing of the duodenal stump closure or of the gastroenteric anastomosis.[10]

In the majority of instances, about 75 to 80 per cent of the stomach was resected. The type of anastomosis done in these cases varied according to the preference of the operating surgeon. The gastrojejunal anastomosis was made either anterior or posterior to the transverse colon, with the stoma varying in size from about 4 cm. to the complete width of the incised stomach. After completion of the gastrectomy, the peritoneal quadrants were thoroughly aspirated to remove digestive juices and food particles. Nonabsorbable suture material was used for wound closure throughout.

After operation nasogastric suction was continued for about two days and then a steadily graduated diet was commenced. For the most part, penicillin and streptomycin were administered both before and for several days following operation. Cultures from the peritoneal cavity, especially where perforation was of less than 12 hours' duration, were frequently sterile. In those instances where sensitivity of the organisms could be determined, the appropriate chemotherapeutic agent was given. In most patients blood transfusions were given either before, after, or during the operation.

RESULTS

In this series of 44 cases of gastroduodenal perforation, there were 41 men. This is not surprising because not only is peptic ulcer more frequent in men, but the incidence of perforation is known to be higher. Interestingly enough, earlier reports[5, 28] on the frequency of the perforation showed a much higher incidence in women than is found today. De Bakey[8] has pointed out also that there is a significantly higher mortality rate in women with gastroduodenal perforation. The fact that in women perforation tends to occur later in life than in men and the fact that gastric perforations, which are more serious than duodenal, are more common in women, may account for the larger number of deaths in women. The three women in this series were 34, 48, and 61 years old, respectively, giving an average age exceeding the mean of the entire group. In figure 1 the cases are grouped according to age in decades. It is noted that almost as many patients were in the sixth decade of life as in each of the three preceding decades. Gastrectomy was successfully accomplished in all of these cases notwithstanding there is a known increase in the mortality rate with increasing age. The one fatality in this series was a woman in the seventh decade of life.

The character and location of the lesion is shown in figure 2. In 42 patients (93.7 per cent) the perforation was a complication of peptic ulcer and usually occurred on the anterior wall of the duodenum. In 1 case the perforation occurred

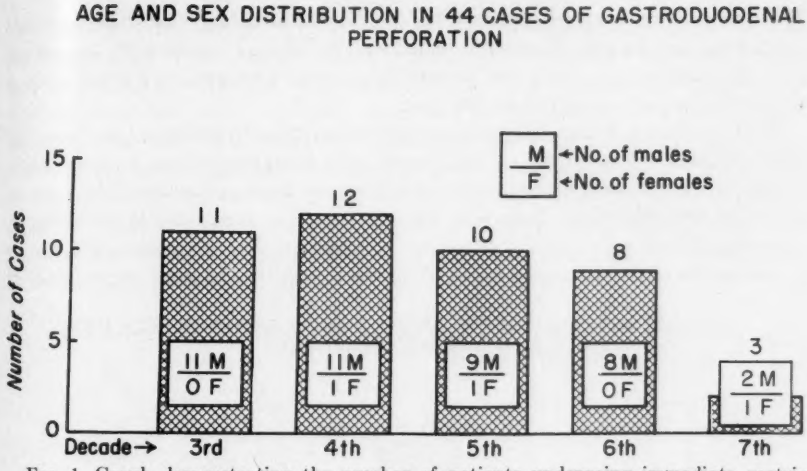

FIG. 1. Graph demonstrating the number of patients undergoing immediate gastric resection in the third through the seventh decades of life and the distribution according to sex. Note that the number of cases is almost as great among patients in the sixth decade as in each of the preceding decades.

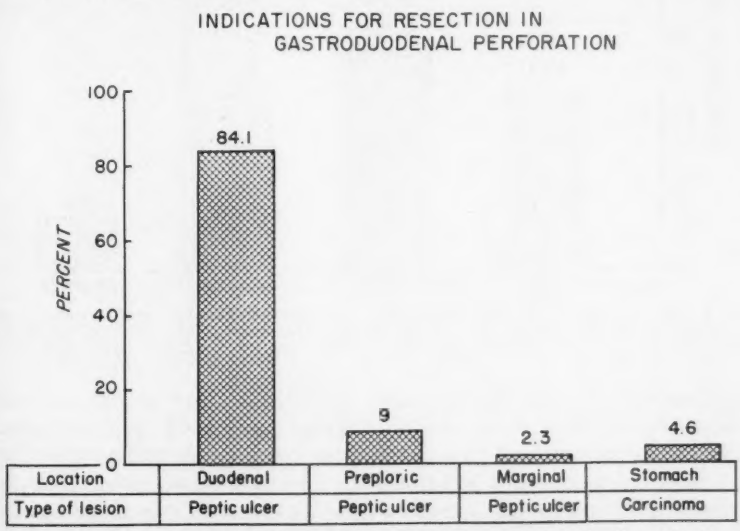

FIG. 2. Graph showing the location of the gastroduodenal perforation in patients undergoing immediate gastric resection. Notice that in 95.4 per cent (42 cases) of the patients, the cause of the perforation was peptic ulcer, while in 4.6 per cent (2 cases) the cause was a perforated gastric carcinoma.

in a marginal ulcer at the site of a previous gastrojejunostomy. In 2 other patients a perforation of a gastric carcinoma was demonstrated. Perforation occurred 12 hours or less prior to laparotomy in over 70 per cent of the patients (fig. 3).

Three cases were operated upon in whom perforation occurred more than 24 hours previously, and in 1 of these the interval was 72 hours. In cases with symptoms over 24 hours in duration, the perforation usually had sealed, leaving only a moderate amount of peritoneal reaction.

Most of these patients tolerated surgery quite well. In general, they fared as well as a similar group of patients undergoing elective gastrectomy. Indeed, many of the patients seemed to have a smoother course after operation with fewer of the usual complications. Ileus was minimal in most cases, and no instance of abscess or subphrenic infection occurred in the group. There was also no instance of disruption of the anastomosis, or of duodenal closure. There were two wound

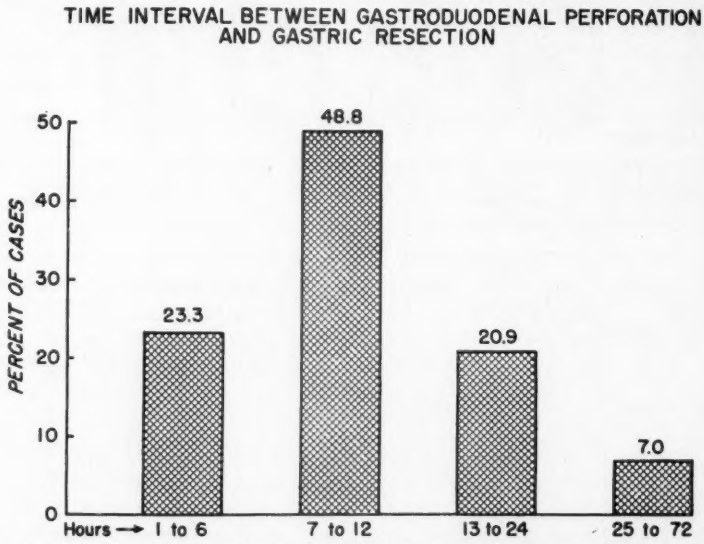

FIG. 3. Graph showing the interval of time which elapsed between perforation and gastric resection in 43 cases treated by immediate gastric resection. Notice that in 72.1 per cent of the patients, the period following perforation was 12 hours or less.

disruptions. One occurred five days after operation in a patient with atelectasis in whom marked efforts to encourage coughing may have played a significant role, and the other occurred a few hours after the completion of surgery. There were 2 cases with mild wound infections, one of which was associated with a small hematoma. The average maximum temperature elevation was about 2 degrees Fahrenheit which ordinarily occurred on the first to third day following operation. Hospitalization was not unduly prolonged, and the duration of hospital stay was usually less than two weeks. From figure 4, it may be seen that a majority of the patients had been discharged from the hospital by the tenth and almost all of the patients by the twentieth day after operation.

There was one operative death in this series giving a fatality rate of 2.3 per cent. This patient was a 61 year old white woman with a history of cardiac dis-

ease with decompensation. The time interval after perforation was difficult to establish. At operation an anterior duodenal perforation was found and there was moderate surrounding peritoneal inflammation. During the preliminary dissection, cardiac arrest occurred, necessitating thoracotomy and cardiac massage. After cardiac resuscitation had been accomplished, gastrectomy was nevertheless completed. The patient did not recover consciousness and died several hours later with convulsions. The effort to proceed with the more extensive operation of gastric resection in the face of such an accident represents an error in judgment. In such circumstances the more conservative procedure of simple closure is indicated.

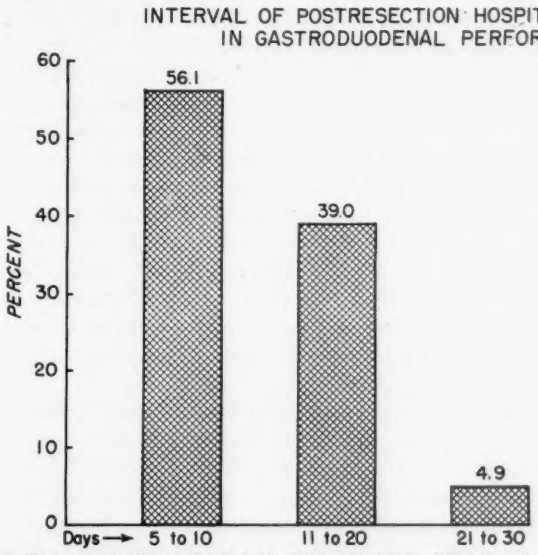

FIG. 4. This graph shows the length of hospital stay following immediate gastric resection for gastroduodenal perforation. Notice that 56.1 per cent of the patients had been dismissed by the tenth day.

COMMENT

Although a policy of immediate gastric resection for acute gastroduodenal perforation of a peptic ulcer would seem to conflict with generally accepted principles of emergency surgery, it is apparent that it offers certain advantages to the patient. If up to 35 per cent of the patients with simple closure will require further surgery for subsequent complications, it is logical to seek a more definitive method of management of the acute perforation. The fact that there was only one death in an almost unselected series of 44 cases operated upon largely by young resident surgeons indicates that gastrectomy does not increase appreciably the risk of surgical treatment in such patients. Another major objection to gastrectomy in acute perforations has been the fear of peritonitis. In light of this experience,

however, this does not appear to be a problem. During the first 12 hours after perforation there is a chemical peritonitis as a result of contamination by gastric and duodenal juices, and after this period has elapsed, bacterial peritonitis ensues. Since no patient in this series developed residual peritoneal injection, it would seem that this complication is controlled by the usual supportive measures and by chemotherapeutic agents.

The performance of the operation has in most instances been facilitated by the inflammatory process around the duodenum rather than made more difficult. In fact, it may be possible in many instances to employ a Billroth I type of resection with gastroduodenostomy, inasmuch as the perforations tend to occur on the anterior duodenal surface leaving the duodenum relatively mobile on the head of the pancreas. There is a current trend toward the more frequent use of this procedure following gastric resection because gastroduodenostomy is usually faster, easier to perform, and minimizes duodenal stump complications, as well as those arising from gastrojejunostomy. From an anatomic and physiologic standpoint this technic is preferable in that it conserves the normal effect of the passage of food down the duodenum which stimulates the flow of pancreatic juice and bile. It has been established that less fat and nitrogen are lost in the stools following a Billroth I procedure[30] and, in addition, according to some,[4, 7, 16, 23, 27] fewer postgastrectomy digestive disturbances occur, such as the *dumping syndrome*. Emphasis is placed on the necessity of an adequate resection of the acid bearing portion of the stomach regardless of the type of anastomosis to be used. In this series the Billroth I procedure has been employed only once, but because of the eminently satisfactory result in this case, and for the reasons already mentioned, we plan to use it much more frequently in the future.

Recently Dodson[9] has reported his experience with so-called *delayed primary resection* for gastroduodenal perforation. According to this plan immediate simple closure of the perforation is done with the intention of performing the gastric resection about three weeks later. This policy during the acute episode was expected to minimize many complicating factors such as dehydration, anemia, and peritonitis. In addition, delay may be advocated in the presence of respiratory and cardiovascular complications, hepatic and renal diseases, obesity, shock, and severe alcoholism. During the interval preceding the final laparotomy and resection, a primed adrenal response occurs, making the patient better prepared physiologically to withstand the larger procedure. During the course of the present study, 9 patients had a delayed primary gastrectomy at periods of 14 to 30 days following the initial closure, and in this group there was one death. We believe that there are some cases in which delayed resection may be preferable, but that, in general, immediate gastrectomy may actually reduce the risk involved in the *staged* procedure.

The only criterion for selection of patients for immediate gastrectomy in this study was based upon the presence or absence of factors contraindicating an extensive surgical procedure. Unless there was evidence of serious cardiovascular, renal, respiratory, or other disturbances, gastric resection was done. This procedure appears to be particularly desirable in younger people, and in patients with

pyloric obstruction, or gastric ulcer, and it may be the procedure of choice in all patients with perforated ulcer unless the contraindications mentioned above are present, providing, of course, as emphasized by Auchinloss,[1] proper facilities and competent personnel exist for its safe performance.

SUMMARY

A series of 44 patients is reported in whom acute gastroduodenal perforation was treated by immediate gastric resection with one death.

In 42 patients (93.7 per cent) the perforation was a complication of peptic ulcer, and in 2 there was a gastric carcinoma.

Perforation preceded gastrectomy by less than 12 hours in 70 per cent of the patients, and in 3 patients the interval was more than 24 hours. A patient in whom 72 hours elapsed prior to operation recovered uneventfully.

Postoperative ileus was minimal and there was no case of residual peritoneal infection or abscess. No instance of disruption of duodenal closure or of gastrojejunal anastomosis occurred.

The duration of hospital stay was in almost all patients less than two weeks.

The results appear to recommend the more frequent use of gastric resection for acute gastroduodenal perforation.

Addendum: Since this paper was submitted for publication 3 additional cases of acute duodenal perforations have been treated with immediate gastric resection. Two of these cases were given a Billroth I resection and all of the cases recovered without complication.

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THE USE OF NOR-EPINEPHRINE IN THE TREATMENT OF HYPOTENSION ASSOCIATED WITH COMMON SURGICAL CONDITIONS

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Hypotension is associated with many surgical conditions and represents a defect in one or more of the factors of blood pressure regulation. Wound shock is the most common situation in which this is encountered. The lowered blood pressure in this condition is due primarily to a reduction in circulating blood volume, the loss having occurred through the wound, into the injured part, or both. The treatment of wound shock is replacement of the lost volume with whole blood, repair of the wound to prevent further blood loss and restoration of normal tissue continuity. Under such circumstances numerous pressor substances can for a time elevate the blood pressure by their specific actions but without sufficient blood circulating through the vital organs, the patient may be unable to withstand the stress of his disease or a necessary operation. Even though survival may be possible, normal hemodynamics will not obtain until the underlying faulty mechanism, *i.e.* the blood volume deficiency, is corrected.

A rarer but not infrequent type of hypotension observed in surgical patients is that due to diminished peripheral resistance. The hypotension that frequently follows thoracolumbar sympathectomy, especially the second stage, is a good example. The blood volume and cardiac apparatus under these circumstances are within normal limits. Other examples include the lowered pressure seen after removal of pheochromocytomas,[4] in severe infections,[1, 6] *spinal shock* following spinal cord injury, and spinal anesthesia. The logical approach to such situations would be to increase the peripheral resistance while directing specific therapy to the cause of the lowered resistance. An effective agent for the maintenance of peripheral resistance has been available since the advent of nor-epinephrine[15, 16] and the value of this drug in maintaining normal cardiovascular equilibrium following sympathectomy has been demonstrated.[5, 9]

Basic work[2, 10] indicates that nor-epinephrine can maintain a normal level of blood pressure by increasing the total peripheral resistance without being accompanied by the vasodilator actions of similar drugs such as epinephrine. This is accomplished by peripheral arteriolar, capillary and venous vasoconstriction. The cardiac output is usually unchanged with its use and the heart rate may be diminished. There is evidence also for increased coronary circulation which can be 20 times the control.[17] This effect has been shown in live swine coronary artery preparations to be due to direct vasodilatory action upon the arterial muscle.[13]

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However, blood flow through such organs as the liver and intestines has been shown to be decreased by the drug due to the increase in the resistance of the splanchnic bed.[3] Decrease in renal blood flow following its use has been noted also.[12, 18]

The method of administration is a simple one. As a rule, 4 mg. of nor-epinephrine* are diluted to 1,000 cc. with 5 per cent dextrose in water or normal saline solution. This solution is given intravenously at a rate determined by the blood pressure response of the patient. The required rate of flow is usually between 10 and 60 drops per minute. The action of nor-epinephrine is rapid and the length of reaction is short so that circulatory control is not difficult.

We have used this drug to maintain blood pressure in cases of *spinal shock*, hypotension from splanchnic block in acute pancreatitis, spinal anesthesia, and infections and have been able to observe its use for hypotension caused by wounds and hemorrhage, dehydration and hyponatremia, and bilateral adrenal hemorrhage (Waterhouse-Friedericksen Syndrome.) Our purpose is to present this experience in order to further confirm the value of this drug and in particular to point out its limitations, contraindications, and complications. This can be done best by using the following cases as illustrations. These are presented in detail.

Case 1. J. K., a 51 year old man, entered the hospital shortly after receiving a shot gun blast through a closed door at close range. Examination revealed an average sized man with multiple small pellet wounds of the neck, thorax, and upper abdomen, a minimal left pneumothorax, paralysis and anesthesia at the level of D_4. The blood pressure was 50/20, pulse 90, and respirations 24. There were no signs of significant internal or external blood loss. The skin was warm, dry and the color of the nail beds and mucous membranes was good.

One thousand cc. of whole blood and 500 cc. of saline solution were given during the first two hospital hours without change in the blood pressure. In the following 34 hours the patient had received a total of 8,500 cc. intravenously (4,000 cc. blood, 4,500 cc. 5 per cent dextrose in distilled water) and had lost 3,925 cc. (1,500 cc. blood, 1,425 cc. urine and 1,000 cc. via levine tube). The blood loss was due to an exploratory thoracotomy for suspected but unconfirmed cardiac tamponade plus free blood in the thorax from the initial injury. After operation blood volume studies indicated a total of 7,800 cc. (112 per cent calculated normal) and a thiocyanate space of 30,303 cc. (180 per cent of calculated normal). This increase in extracellular fluid volume was evident clinically by pitting edema. During this period of over replacement therapy the patient's blood pressure did not rise above 50/20 until nor-epinephrine was given. Nor-epinephrine solution (4 μg/cc.) was given at a rate of 18 to 20 drops per minute from the second hospital hour for a total of 53 hours. The nor-epinephrine solution was discontinued intermittently for brief intervals during this period but at no time would the blood pressure remain above the hypotensive levels.

The blood pressure stabilized on the third day and the patient was able to consume a soft diet on the fourth day. At this time roentgenograms showed a pellet within the spinal canal at the level of D_4. Lumbar puncture showed normal spinal fluid pressure and dynamics but the fluid was xanthochromic and contained many crenated red blood cells. The patient continued to improve and was discharged on the twenty-second day for paraplegic rehabilitation.

This patient sustained a marked loss of peripheral resistance due to spinal cord injury. His blood pressure did not respond to vigorous replacement therapy, even carried to the point of overhydration. His response to nor-epinephrine was

* Levophed-Winthrop-Stearns Co.

dramatic, and the drug was effective in maintaining blood flow until sufficient vascular tone was regained to provide circulatory homeostasis.

Case 2. V. W., a 30 year old married woman, had had attacks of upper abdominal pain intermittently for one year. This pain would frequently be referred to the back and could be precipitated by the ingestion of fatty foods. Twenty-four hours before admission, the patient developed severe intermittent upper abdominal pain that radiated through to the back and toward both scapulas. There was associated anorexia, nausea and vomiting but no chills, jaundice, or change in color of either stools or urine was observed.

Physical examination revealed a slightly obese moderately dehydrated woman. The temperature was 99F., pulse 86, and blood pressure 150/100. The abdomen was diffusely tender, being greatest across the upper abdomen and extending into both flanks. There was marked spasm and rebound tenderness in this region. Laboratory data included a normal urinalysis, 14 Gm. per cent of hemoglobin, 20,900 white blood cell count and serum amylase 223 mg. per cent (normal 40–60 mg. per cent).

A diagnosis of acute hemorrhagic pancreatitis was made and the patient begun on a program of naso-gastric suction, atropine subcutaneously, penicillin, parenteral fluids and analgesics. During the next 18 hours approximately 600 cc. of fluid were aspirated through the nasogastric tube and the patient received 2,000 cc. of 5 per cent dextrose in distilled water. At the end of this time, however, her condition was much worse. The blood pressure dropped to 50/40, she became stuporous, with rapid shallow respirations. The pulse was rapid and weak. Profuse perspiration was present. Dehydration was evident by dry mucous membranes, soft eyeballs, and loss of normal skin turgor, and was thought to be the cause for the hypotension. Fluids were increased and during the next six hours the patient received an additional 3,500 cc. (2,000 cc. 5 per cent dextrose in saline, 1,000 cc. 5 per cent dextrose in water, 500 cc. whole blood) intravenously with rapid and sustained improvement in her condition. Her 24 hour urine output was 800 cc.

By the second hospital day the patient's general condition seemed good even though the abdominal findings were unchanged. Abdominal pain continued to be severe and uncontrolled with frequent injections of demerol. A splanchnic block was performed using 40 cc. of 1 per cent novocaine with relief of pain; however, the blood pressure dropped to 0/0. The rate of flow of the fluids was increased but this was followed by little increase in blood pressure. Blood volume studies at this time revealed a total of 5,196 cc. (calculated 100 per cent of normal). A solution of nor-epinephrine (1,000 cc. 5 per cent dextrose in saline containing 4 mg. nor-epinephrine) was begun and given at a rate of 20 drops per minute. The blood pressure was well maintained as long as this solution was given but upon reducing the flow the blood pressure would drop. This sequence continued for six hours at which time the blood pressure remained at a normal level after discontinuing the solution. The urinary output for this day was 1,300 cc.

The patient had no further hypotensive episodes, the abdominal signs slowly subsided and the serum amylase decreased to normal. A Graham-Cole test done after the disease became quiescent showed no filling of the gallbladder. A chronically inflamed gallbladder filled with stones was removed as an interval operation, with uneventful recovery. The pancreas was diffusely indurated and slightly enlarged.

The right femoral vein was selected for injection of the nor-epinephrine solution because of general collapse of peripheral veins during the hypotensive episode. Twenty-four hours later a palmed-sized blotchy red area was seen at the sight of injection that underwent vesicle formation by the fourth day (fig. 1). Gradually the skin and subcutaneous tissues sloughed and secondary wound closure was required.

This patient demonstrates the loss of peripheral resistance and hypotension which may occur following splanchnic block in a patient suffering acute pancreatitis. A normal blood volume was observed denoting adequate fluid replacement

therapy. She responded satisfactorily to nor-epinephrine therapy which was required for approximately six hours during which time the effects of the procaine receded and the vascular tone of the splanchnic bed was resumed.

The slough of tissue at the injection site is attributed to extravasated nor-epinephrine solution. This phenomen has been noted by others,[6, 15, 16] and is thought to be due primarily to intense local vasospasm.

Case 3. P. M., a 57 year old man, was admitted to the Jefferson Davis Hospital because of anemia, weight loss, and ankle edema. Roentgenologic examination revealed a carcinoma high in the stomach. The patient's hemoglobin was restored to normal and a transthoracic partial gastrectomy was performed with adequate blood replacement. His temperature

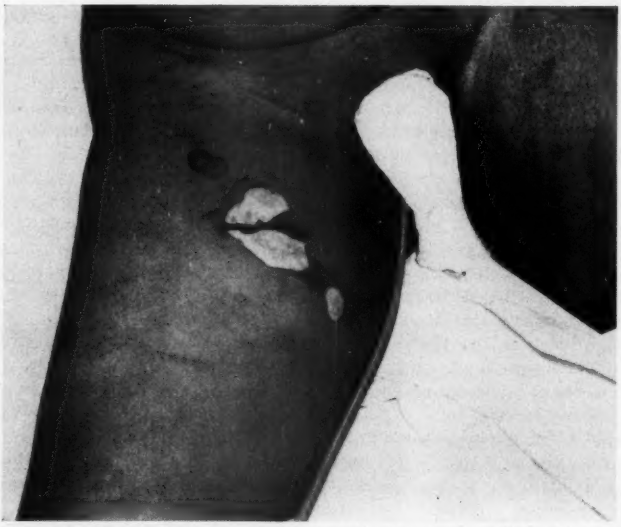

FIG. 1. This patient sustained an area of skin and subcutaneous tissue slough following 6 hours of nor-epinephrine therapy via the femoral vein. Secondary wound closure was subsequently required.

ranged between 100 F. and 104 F. during the first four postoperative days, and was associated with atelectasis. Notwithstanding an adequate fluid intake and urinary output and without signs of blood loss he developed hypotension on the second day. This was treated for 24 hours with a continuous drip of nor-epinephrine solution maintaining a normal preoperative blood pressure.

Toward the end of this period the patient's temperature decreased, but remained elevated. Nor-epinephrine was discontinued, and blood pressure was well maintained. Gradually, however, he developed jaundice, pain and tenderness in the right upper abdominal quadrant. These signs of intra-abdominal infection became greatest on the tenth postoperative day. The blood pressure at this time without evidence of blood loss or dehydration dropped to 90/60. Blood volume studies revealed a normal value, a slightly increased thiocyanate space, and a hematocrit of 57 per cent. In view of the normal blood volume, nor-epinephrine solution was administered and a normal blood pressure was maintained.

Several hundred cc. of foul smelling yellowish pus was drained from the right upper quadrant under local anesthesia. Following this operation, the patient's condition remained

poor with elevated temperature and diffuse signs of peritonitis. Large doses of antibiotics were given and nor-epinephrine solution was required continuously throughout the following seven days until the patient died. Throughout this period, the urinary output averaged 1,500 cc. per day.

The nor-epinephrine solution was given through a polyethylene catheter which had been threaded about 25 cm. up the saphenous vein from the ankle. There was no obvious leak but an area of gangrene developed along the course of the vein almost to the knee.

Postmortem examination revealed a diffuse peritonitis with a large drained abscess in the right upper quadrant in the region of the duodenal stump which appeared closed.

Hypotension was due to loss of peripheral resistance secondary to a severe peritonitis and intra-abdominal abscess in an elderly debilitated man. Assured that a diminished blood volume did not exist, though hemoconcentration was evident, nor-epinephrine was given and was able to maintain the blood pressure and urinary output within a normal range for seven days continuously.

Since a polyethylene catheter was threaded into the saphenous vein, extravasated nor-epinephrine solution would not appear to be the reason for the tissue slough. This and similar experiences strongly suggest that prolonged intravenous administration can of itself produce local tissue destruction. This tendency might be augmented by the reduced peripheral blood flow in shock, and by the reduction in blood flow through the vein used to administer the solution caused by ligation of the vein distal to the cannula.

Case 4. E. H., a 52 year old woman, entered the hospital complaining of abdominal pain Five days before admission the patient was seized after eating by mid-abdominal cramp-like pain which radiated into both upper and lower quadrants but not into the back. Several hours later the patient felt something burst and subsequently the pain became localized to the right upper quadrant. There was associated nausea, vomiting, and constipation. There was a sensation that a bowel movement would relieve the pain and several enemas were taken but without relief. Even though there had been little appetite, the patient had consumed a soft diet throughout this illness.

Examination revealed an acutely ill moderately dehydrated woman in considerable distress. Her blood pressure was 160/70, pulse 120, temperature 101 F. and respirations 24. The abdomen was diffusely tender and spastic, more marked in the right upper quadrant. Pelvic and rectal examinations were normal. Peristaltic sounds were heard. Laboratory data included a normal urinalysis, white blood cell count 17,200, hemoglobin 12 Gm. per cent, and serum amylase 18 mg. per cent.

A nasogastric tube was inserted into the stomach and attached to suction. Penicillin and streptomycin were given intramuscularly and intravenous fluids instituted.

Three hours later, having received 2,500 cc. (1,000 cc. 5 per cent dextrose in saline and 1,500 cc. 5 per cent dextrose in water) the patient was operated upon using gas-oxygen-ether anesthesia. An acutely inflamed appendix lying under the lower edge of the liver was found. There was a surrounding abscess which extended into the anteriorsuperior subdiaphragmatic space. The abscess was inadvertently entered and about 500 cc. of greenish-yellow pus was spilled into the general abdominal cavity. The pus was aspirated and after the perforated appendix was removed, the subdiaphragmatic space and the right gutter were drained through a lateral stab wound. Even though there was little blood loss, the blood pressure fell to 80/60 toward the end of the operation. Five hundred cc. of blood and 650 cc. of 5 per cent dextrose and water were given rapidly without change in the blood pressure. Blood volume and extracellular space studies done at this time (total blood volume 6,021 cc. and thiocyanate space 20,747 cc.) were within normal limits. The lowered blood pressure was thought to be due to a lowered peripheral resistance therefore, a nor-epinephrine solution

(12 mg. in 1,000 cc. of 5 per cent dextrose in water) was begun and regulated so that the preoperative blood pressure was maintained. In order to maintain blood pressure, nor-epinephrine was required for the subsequent 24 hours. During this time, 1,600 cc. 5 per cent dextrose in saline and 500 cc. of blood were given. The urine output for 24 hours was 500 cc. The average intake for the following 2 days was 3,500 cc. and on the fourth day oral feedings were begun. The urine output averaged 800 cc. per day during this period. The temperature ranged between 102 F. and 104 F. for the first three days but by the fourth day it dropped to 99 F. and was normal on the sixth day. Signs of peritonitis subsided along with the temperature, and the patient recovered satisfactorily.

This case illustrates hypotension due to a peritoneal deluge of pus, causing a marked loss of peripheral vascular resistance. The blood volume was demonstrated to be normal. Nor-epinephrine was effective in maintaining circulatory efficiency for 24 hours at which time peripheral vascular tone had improved so as to produce circulatory compensation.

Case 5. N. S., a 52 year old man, received a transurethral resection for benign prostatic hypertrophy. Thirty Gm. of tissue were removed in 1 hour and 40 minutes. Twelve hours prior to surgery, 500 cc. of whole blood were given to correct an anemia evident by 9.7 Gm. per cent hemoglobin and 3,310,000 red blood cells. The operation was accompanied by a little more than usual blood loss. The blood pressure remained stable at 110/70 throughout the procedure. Five hundred cc. of whole blood was started at the end of the operation and the patient was returned to the ward in good condition.

One hour after the operation, while receiving the last of the transfusion, the blood pressure was 80/60. This was associated with the usual peripheral signs of shock. The patient was placed in shock position and 1,000 cc. of 5 per cent dextrose in water were given after the above transfusion. Over the course of the succeeding three hours, the blood pressure ranged between 70/50 and 98/60. Five hundred cc. of whole blood and 1,000 cc. of nor-epinephrine solution (4 μg. per cc.) were begun intravenously. Subsequently, a normal blood pressure could be maintained by regulating the flow of nor-epinephrine from 10 to 20 drops per minute. This was done for 24 hours with 3,000 cc. of solution.

Throughout this period the catheter drained bloody urine and 6 hours following surgery 1,100 cc. of blood, urine and clots were removed from the bladder. Nor-epinephrine was discontinued 24 hours followng the beginning of its administration. This was followed by a blood pressure drop to 78/0. The general pallor that was constantly present continued as well as signs of diminished peripheral circulation. Whole blood was then infused and the patient received 2,000 cc. over the course of eight hours. The blood pressure rose to normal toward the latter part of this period and remained so throughout his subsequent hospital stay. The improvement in blood pressure was associated with increase in color and the disappearance of the signs of shock. His subsequent urological convalescence was uneventful, however, an 18 cm. by 10 cm. area in the anticubital fossa surrounding the site of nor-epinephrine injection, sloughed and required a skin graft (fig. 2).

This patient demonstrates the fallacy of treatment of hypotension due to continuing hemorrhage by nor-epinephrine. In this instance, blood loss during and after surgery was considerable and blood replacement inadequate. In spite of a reduced blood volume, nor-epinephrine was able to maintain a relatively normal blood pressure, but whole blood was required before the circulation could stabilize satisfactorily. The tissue slough is doubtless due to the prolonged local action of a potent vasoconstrictor and the diminished blood flow associated with shock. It is probable that had this patient received adequate blood replacement early, shock would have been alleviated and the tissue slough at the injection site avoided.

Case 6. A. N., a 67 year old man, entered the Jefferson Davis Hospital because of intermittent upper abdominal pain of two days' duration, associated with anorexia, nausea and considerable vomiting. He had had one bowel movement and had passed little urine. Physical examination revealed an obviously ill, severely dehydrated, and slightly disoriented man with blood pressure of 150/90, pulse 136, and oral temperature of 99.9 F. The abdomen was slightly distended but diffusely tender, more marked across the upper abdomen. A routine urinalysis was normal. The hemoglobin was 14.5 Gm., white blood cell count 7,650 and serum amylase 82 mgm. per cent.

The patient was admitted with a diagnosis of acute pancreatitis and was placed on a program of nasogastric suction, atropine, penicillin and analgesics. 2,000 cc. of pinkish fluid were removed from the stomach. Very soon after admission the blood pressure fell to 90/60, associated with cyanosis of lips and nail beds. In order to correct the cyanosis and hypotension oxygen was begun by nasal catheter and nor-epineprine solution (12 mg. per

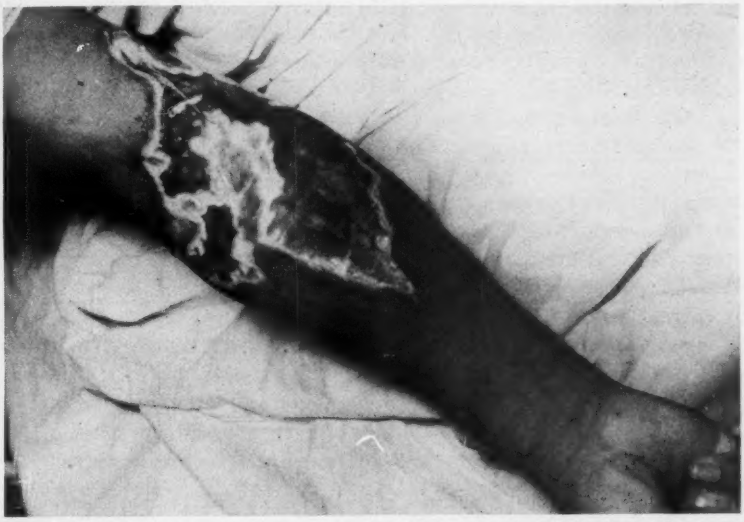

FIG. 2. A 10 by 18 cm. area in the antecubital fossa sloughed following 24 hours intravenous nor-epinephrine therapy. An extensive skin graft was required to close the wound.

650 cc. saline) was started intravenously. The latter was given at a rate that maintained the blood pressure at 120/80. For approximately 48 hours, however, the patient continued to deteriorate and died at the end of this time. The fluid intake and output during this illness are shown on Table 1. The urea nitrogen was 163 mg. per cent, sodium chloride 106 MEQ/L; CO_2 11.5 MEQ/L, serum sodium 120 MEQ/L; serum potassium 4.5 MEQ/L. Postmortem examination showed an extremely dilated stomach with severe giant rugal gastritis and a normal pancreas.

This case illustrates the fallacy of using nor-epinephrine to treat hypotension due to hyponatremia and dehydration. It is apparent from Table 1 that not only was the initial fluid deficit not replaced, but an additional sodium deficit was acquired, since saline replacement did not equal gastric drainage. Since the low blood pressure was due to a decrease in salt and water content of the blood, increasing peripheral resistance by the use of nor-epinephrine was only partially

successful early and subsequently failed completely to maintain circulation in the face of a continued fluid and electrolyte deficit.

Case 7. R. R., a 29 year old woman, who was four months pregnant, entered the hospital complaining of lower abdominal cramps of a few hours' duration. At the time of admission she did not appear acutely ill even though her temperature was 104F. The blood pressure was normal. There was lower abdominal tenderness in the region of the uterus. The cervix was moderately dilated but there was no blood in the vagina. Routine blood and urine examinations were normal except for elevated white count.

A diagnosis of septic abortion was made and antibiotics and intravenous fluids were instituted.

Five hours after admission the patient's general condition had become worse, blood pressure was 86/50 and pulse 100, and was associated with profuse sweating. One thousand cc. of whole blood were given rapidly without improvement. During this time a macerated foul-smelling fetus was passed. The total blood loss during delivery did not exceed 500 cc.

TABLE 1

	Intake	Output
	First 24 hours	
	3,000 5% dextrose in saline 1,000 5% dextrose in water 500 whole blood	2,800 gastric drainage 400 urine
Total	4,500 cc.	3,200 cc.
	Second 24 hours	
	1,000 5% dextrose in saline 3,000 5% dextrose in water	1,700 gastric drainage 800 urine
Total	4,000 cc.	2,500 cc.

Even so, 500 cc. of additional blood were administered rapidly. The blood pressure soon became unobtainable whereupon nor-epinephrine solution was given intravenously with no response even though a concentration of 1 mg. per cc. was finally used. The patient died 11 hours after admission and postmortem examination showed that both adrenal glands were markedly hemorrhagic.

Though a fulminating septicemia was not proved in this case, the rapid febrile course, marked shock, and adrenal hemorrhage suggest the Waterhouse-Friedericksen Syndrome of acute adrenal insufficiency. Neither blood nor nor-epinephrine was effective under these circumstances.

DISCUSSION

Cases 1 and 2 are examples of hypotension due to lowered peripheral resistance. The blood and extracellular fluid volume of both were normal or increased during the period of hypotension; in fact, case 1 had markedly elevated values. The lowered resistance of both was due to the disruption of the nervous control of the peripheral vascular organ and both responded satisfactorily to the administration of nor-epinephrine. The advantages of the drug in such cases are well shown in the

first patient. The intravascular and interstitial spaces were already expanded to the point of clinical edema and to crowd these spaces further in order to raise the blood pressure might have induced pulmonary edema and disaster. It is also of interest that this drug used successfully for 53 hours during which time the urine output was entirely adequate.

It is well known that hypotension can exist in the presence of a normal blood volume and cardiac action in patients suffering severe infections. Case 3 is an instance where infection was the dominating factor in the hypotension. This patient had a slightly elevated blood volume, extracellular fluid volume, and hematocrit. The heart was normal. Hypotension, nevertheless, prevailed. An essentially normal cardiovascular performance was maintained for several days with the administration of nor-epinephrine solution. During this time the urine output was adequate. The administration of further fluids in this case would possibly have caused pulmonary edema and would not have improved the blood pressure. However, the cause of the lowered pressure in similar cases is rarely due to diminished peripheral resistance from infection alone. There is usually a marked decrease in circulating blood volume caused by an outpouring of a plasma-like fluid into the peritoneal cavity. This insult resulting in massive transudation has been likened to a peritoneal burn.[14] It is the experience of many observers that large quantities of colloid solution (blood and/or plasma) are necessary to restore equilibrium to the cardiovascular apparatus as in the burn patient. It seems likely that nor-epinephrine prolonged this patient's life. In this instance it was of no avail, but in similar cases proper surgical drainage and antibiotic therapy may be more effective in eliminating the cause for the lowered peripheral resistance while nor-epinephrine maintains adequate circulation to the vital organs and insures proper fluid and electrolyte balance by maintaining renal function. The hypotension in case 4 was not due to whole blood or plasma loss but resulted primarily from a diffuse peritoneal insult from the spillage of pus. Nor-epinephrine successfully maintained normal cardiovascular function for the 24 hours during which hypotension prevailed.

Case 5 illustrates the use of nor-epinephrine in shock from hemorrhage. It is apparent that this patient lost considerable blood during and after operation which was inadequately replaced. Nevertheless, a nor-epinephrine solution maintained a blood pressure comparable to the value before operation. It is significant, however, that this patient's blood pressure did not stabilize at a normal level until the lost blood had been replaced. Temporary survival was possible as a result of nor-epinephrine therapy, but control of hemorrhage and replacement of lost blood were required before resuscitation was complete. To increase the peripheral resistance in the presence of the diminished blood volume will markedly decrease the blood flow in such organs as the intestines and the liver.[3, 7] This is an undesirable sequence of events and is an unphysiologic approach to the treatment of shock from this cause. It is evident that whole blood transfusion was the indicated treatment, and had this been carried out the patient would have been physiologically normal 24 hours earlier and would have been spared the complication of an antecubital slough. This complication occurs frequently with the continued use of nor-epinephrine in shock patients.

In case 6, the underlying mechanism producing hypotension was hyponatremia and lowered circulating blood volume secondary to dehydration. These deficits, unfortunately, continued during his hospital stay because of inadequate replacement therapy. Nor-epinephrine was able to maintain a normal blood pressure even in the face of this marked physiologic alteration. The outcome of this case emphasizes the rather obvious point that dehydration and hyponatremia are not satisfactorily treated by vasoconstriction by a vasopressor drug.

Case 7 is included to indicate the inadequate action of the drug in a case of hypotension due to the Waterhouse-Friederichsen syndrome. Very concentrated solutions were used without beneficial results. It would appear that the shock in this case was due to factors other than blood loss or diminished peripheral resistance. The adrenal cortex was markedly hemorrhagic and presumably functionally incompetent.

In our experience, prolonged subcutaneous injection of nor-epinephrine is followed routinely by extensive tissue slough, therefore extravasation must be avoided. With prolonged intravenous use, the local tissue destruction at the injection site has also been quite high. In our opinion, the problem is primarily that of intense local vasospasm from intravenous diffusion of the agent. This action is intensified by factors which tend to limit dilution of the drug by the blood, *i.e.* reduced peripheral blood flow as in shock, and occlusion of the vein by ligation distal to the site of injection. Rotation of the site of injection every 12 hours has been helpful, and should be practiced whenever possible. Injection of the solution through a polyethylene tube at a point where blood flow is considerable offers a more rapid diluting effect and thus some protection against sloughing. Theoretically, injection into the inferior vena cava via a long polyethylene tube would appear to be advantageous for protracted therapy. We have administered the solution into the femoral vein by per-cutaneous catheterization on one occasion for a period of approximately five hours, and postmortem examination revealed no gross evidence of venous or surrounding tissue injury. Further work is desirable to find some means of avoiding local destruction of tissue. Until this can be done, nor-epinephrine must be used only upon precise indication, with attention to avoidance of local tissue slough.

SUMMARY

1. Examples of our experience with the use of nor-epinephrine in the treatment of hypotension associated with several common surgical conditions are presented.

2. The indication for the use of nor-epinephrine is hypotension due to diminished peripheral vascular resistance. This situation is encountered in spinal anesthesia, so-called spinal shock, severe surgical infections such as peritonitis, following extensive sympathetomy, removal of pheochromocytomas, and following splanchnic block in acute pancreatitis. Successful and sensible use of the drug is predicated upon assurance of a normal circulating blood volume.

3. Contraindications include any surgical condition where hypotension is not due to lowered peripheral resistance. It is especially emphasized that nor-epinephrine is contraindicated in wound shock and fluid electrolyte deficiency states such as dehydration and hyponatremia in which a characteristic blood volume and

component deficit occurs. The use of nor-epinephrine in blood volume deficiency states is especially treacherous since it is temporarily effective in elevation of blood pressure, and may mask the seriousness of the situation. Rational physiologic treatment demands blood volume replacement for blood volume lost.

4. Complications encountered in our experience are: (1) local tissue slough from prolonged intravenous administration or subcutaneous extravasation. (2) tendency to overhydration by giving the patient a constant drip of nor-epinephrine solution, particularly if oliguria or anuria complicates the shock problem. We recommend rotation of the site of intravenous injection every 12 hours, if possible, to minimize the local vasoconstrictor effects. Injection of the drug at a point where venous flow is considerable offers a more rapid diluting effect and thus some protection against tissue destruction. Because of the frequency with which local tissue slough follows the prolonged use of the nor-epinephrine in shock, the indication for its use must be precise, with special attention paid to its local injection.

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SUCCESSFUL RESECTION OF MYCOTIC ANEURYSM OF SUPERIOR MESENTERIC ARTERY

CASE REPORT AND REVIEW OF LITERATURE*

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Control of aneurysms has challenged surgeons since earliest times. Interest has centered chiefly around those aneurysms involving the aorta or its major tributaries which are caused by syphilis, arteriosclerosis or trauma. Mycotic aneurysms have received less attention from the surgeon, as these lesions are encountered relatively infrequently and the usual predisposing diseases, subacute bacterial endocarditis or septicemia, have been prone to progress to a fatal termination or to leave the patient so hopelessly crippled that surgical intervention was impossible.

Aneurysms involving the superior mesenteric artery are relatively rare. Although their exact incidence is difficult to determine, some idea of their infrequency may be obtained from some of the recorded statistical studies on aneurysms. In the collected series of 551 aneurysms compiled by Crisp,[10] in 1847, there was not a single instance of involvement of the superior mesenteric artery. Similarly in Matas'[33] series of 172 cases of aneurysm at Charity Hospital in New Orleans, during the 10 year period, ending in 1905, none involved the superior mesenteric artery. Saleeby and McCarthy[42] also found none involving this vessel among 84 patients with aneurysms admitted to the surgical wards of the Philadelphia General Hospital during the 32 year period, 1904 to 1936. In his analysis of 142 cases of aneurysms admitted to the surgical service at the Johns Hopkins Hospital from its opening to January 1922, Reed[39] found only 1 with involvement of the superior mesenteric artery. In an analysis of 19,300 autopsies at the General Hospital in Vienna, Von Schroetter,[45] in 1901, reported 220 cases with aneurysms only 1 of which involved the superior mesenteric artery. A somewhat similar incidence was observed by Lucke and Rea[31] (1 case among 268 subjects examined with aneurysms in 12,000 necropsies) and by Garland[17] (1 case among 167 subjects with aneurysms in 12,000 consecutive autopsies).

Whereas among all aneurysms involvement of the superior mesenteric artery is relatively rare, in mycotic aneurysms this vessel is one of the sites of predilection. Thus, in a collected series of 92 mycotic aneurysms in 65 patients, Lewis and Schrager[29] found 25 located in the superior mesenteric artery. In Stengel and Wolferth's[49] collected series of 264 mycotic aneurysms in 217 patients, 24 involved the superior mesenteric artery, being second in frequency to the aorta which was involved in 66 instances. In Scott's[46] analysis of 115 abdominal aneurysms of all types at the Johns Hopkins Hospital, the most frequent sites of occurrence was the aorta in 68 cases and the next most frequent sites were the supe-

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rior mesenteric and splenic arteries, each of which was involved in 11 cases. Among the 21 mycotic aneurysms in this series the superior mesenteric and hepatic arteries were most commonly affected with 5 involving the former and 6 the latter vessel.

In 1901, Gallavardin[16] collected from the literature 23 cases of aneurysms of the superior mesenteric artery and in 16 of which the etiology could be established 9 were considered mycotic.

Up to 1930 Helwig and Wilhelmy[20] were able to collect only 25 cases of mycotic aneurysm of the superior mesenteric artery, and added 3 cases of their own. In 1944, Laufer and Smith[26] brought this number up to 30. In a careful search of the literature beginning as early as 1830, Hedinger[19], in 1947 was able to tabulate only 35 cases including 1 of his own. A further search of the literature reveals 29 additional cases, 20 of which were mycotic,[8, 9, 13, 23, 26, 28, 29, 32, 37, 41, 46-48, 54] 8 syphilitic,[3, 46, 58] and 1 of undetermined etiology,[18] making a total of 63 cases reported up to date. Although a few of these cases were diagnosed during life and 7 had surgical intervention, none was successfully treated. It seems desirable, therefore, to report the following case of a mycotic aneurysm of the superior mesenteric artery which was diagnosed preoperatively and successfully resected.

CASE REPORT

Mrs. D. L., a white housewife aged 27 years, was first seen May 1949, complaining of dyspepsia and a dull aching pain of 5 months' duration in the upper part of her abdomen. Four years previously, about one week following the birth of her only child, the patient had an attack of chills and fever, weakness and general malaise. This was diagnosed as *subacute bacterial endocarditis* by her physician, who had noted a cardiac murmur on prenatal examination. The patient was admitted to the hospital where the diagnosis of subacute bacterial endocarditis was confirmed by positive blood cultures, and intensive therapy with penicillin was instituted. After a few weeks the penicillin was supplemented by streptomycin for a period of approximately 10 days. During this time she developed one episode of multiple peripheral emboli including one of the right retinal vessels. After several months of treatment, she left the hospital to return to her home town, where the penicillin therapy was continued for several more months. In 1947, after 18 months of almost continuous treatment with antibiotics, she was told that she was cured. Shortly thereafter, she began to notice vague digestive disturbances with mild pain in the epigastrium and upper lumbar region. In January 1949, when the pain became more severe and she began to have increased postprandial distress and persistent constipation, she consulted a physician who treated her symptomatically without improvement. In March 1949, an exploratory laparotomy was done because of a small mass in the upper part of the abdomen. The mass, which was pulsatile in character, was located near the midline below the stomach. It was considered to be an aortic aneurysm. No attempt was made to deal with it and the abdomen was closed. The patient was told that she had a *blood vessel tumor* and that further surgical therapy would be required.

The patient gave no definite history of rheumatic fever but she remembered distinctly that she had had rather severe *growing pains* in childhood. Prior to onset of the present illness, dyspnea, edema, or other manifestations of cardiac decompensation were not noted. She had always been considered to be somewhat *delicate*.

Physical examination revealed a well developed, nervous, malnourished white woman appearing to be her stated age. The heart was definitely enlarged; the apex beat was in the sixth interspace just inside the anterior axillary line. The pulse rate was 80 per minute with a regular sinus rhythm. A loud blowing systolic murmur was heard over the entire precor-

dium, loudest at the apex. Her blood pressure was 130/90 and her lungs were clear and resonant.

The abdomen was flat. There was a healed infra-umbilical midline scar. A slightly tender ovoid mass was palpable just to the right of the midline, midway between the ensiform cartilage and the umbilicus. The mass measured approximately 6 cm. in its greatest diameter. It could be felt to pulsate and the pulsation was synchronized with the heart beat. The mass could be moved easily from side to side for a distance of 3 or 4 cm. Auscultation revealed a distinct systolic bruit. The femoral pulses were full and bounding.

Roentgenogram of the chest on admission to the Methodist Hospital showed pronounced cardiac enlargement with definite right ventricular hypertrophy. The white blood cell count was 6,950 per 100 cc. with normal distribution and the red cell count was 4,280,000 per 100 cc. There were 13.0 Gm. of hemoglobin per 100 cc., and the hematocrit was 36 per cent. The bleeding and coagulation times were 2 minutes 30 seconds and 4 minutes 10 seconds, respectively. The Kahn reaction was negative. Urinalysis showed specific gravity of 1,030, acid reaction, 2 plus albumin, and no sugar. Microscopic examination of urinary sediment revealed many epithelial cells and moderate mucus. Because of the history of subacute bacterial endocarditis, administration of 100,000 units of penicillin every 3 hours was started on admission.

Tentative diagnoses of well compensated rheumatic heart disease, arrested subacute bacterial endocarditis, and mycotic aneurysm of the superior mesenteric artery were made.

On May 20, 1949, with the patient under spinal and light pentothal anesthesia, the abdomen was opened through a right paramedian incision, extending from the ensiform cartilage to just below the umbilicus. The tumor, which had been palpated preoperatively, was located in the region of the lesser peritoneal sac. When the sac was opened through the gastrocolic omentum, the mass came into view. Its expansile character was confirmed, and a definite thrill was palpable.

The aneurysm involved the superior mesenteric artery beginning at a point just below the inferior border of the pancreas (fig. 1). It was about 5 cm. in diameter and 8 cm. in length and was firmly adherent to the surrounding structures. The artery just above the aneurysm was freed and a heavy silk ligature to be used for traction and control of hemorrhage was passed around it. The ligature was not tied but traction upon it completely occluded the artery. The artery was occluded for 5 minutes by traction upon the encircling ligature without causing any appreciable color change in any portion of the intestine. It was therefore decided that resection of the entire aneurysm was feasible. Dissection was done by following the wall of the sac closely at all times. Each vessel was individually ligated and divided as it was encountered.

The superior mesenteric vein was intimately adherent to the wall of the sac and partially occluded by the surrounding fibrous tissue. In order to free it from the sac it was ligated and divided. Immediately following this a portion of the small intestine became slightly dark in color and the mesenteric veins in this region appeared distended but the intestine remained viable. When the aneurysm had been completely dissected free, the superior mesenteric artery was doubly ligated and divided proximal and distal to the sac, and the entire aneurysm was removed. The opening in the mesentery was closed with interrupted sutures and the abdomen was closed in layers with interrupted sutures of cotton.

The patient left the operating room in good condition. She was discharged from the hospital on the eighth postoperative day after an uneventrul postoperative course.

The aneurysm measured 5.2 by 4.5 by 4.5 cm. The stump of the superior mesenteric artery on the proximal side of the sac was of normal size. At least 5 major branches were observed making their exits from the lateral and distal part of the sac. Embedded in loose connective tissue on one surface was a segment of superior mesenteric vein measuring 5 cm. in length. On section the lumen was almost globular and partially filled with a firm gray thrombus which measured up to 1.5 cm. in its greatest thickness. The wall varied from 0.3 to 0.5 cm. in thickness. The lining was dense, pearly gray with large flat atheromatous areas.

The microscopic section included the aneurysm wall and a segment of the thrombus. The

internal portion of the thrombus had a loose fibrinous structure with a few incorporated white cells and moderate numbers of erythrocytes enmeshed in the fibrin. The portion attached to the lining consisted of dense hyalin material in which there were irregular spaces, which apparently contained a lipoid material, and phagocytes laden with lipoid. The aneurysm wall consisted of dense hyalin, fibrous connective tissue which was relatively poor in nuclei. There was a moderate leukocytic infiltration consisting mainly of lymphocytes around the blood vessels.

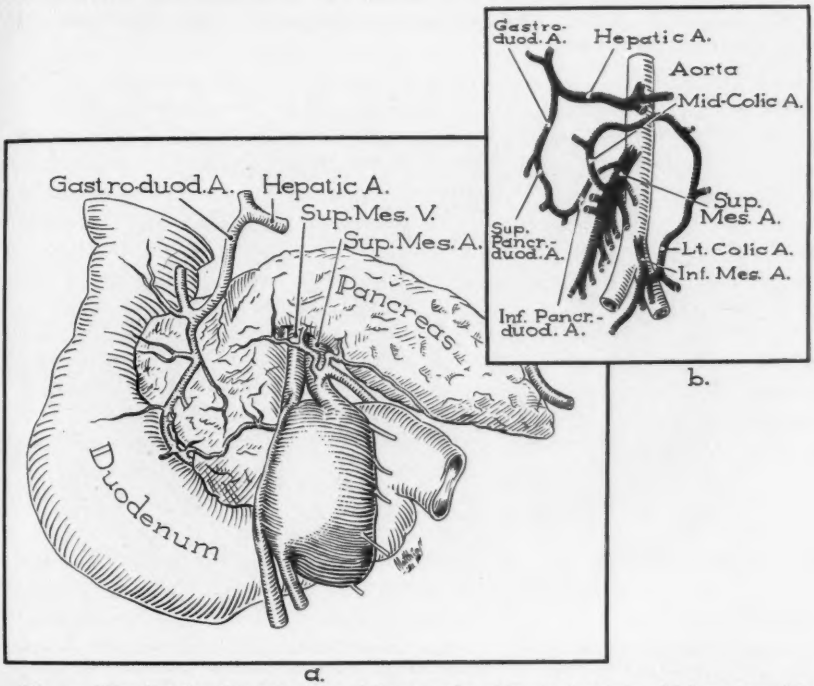

FIG. 1a. Drawing showing aneurysm of the superior mesenteric artery which measured 5 cm. in diameter and 8 cm. in length. Ligation of the mesenteric artery proximal and distal to the aneurysm with division of small branches permitted complete removal of the lesion. The mesenteric vein which was almost totally occluded was likewise doubly ligated and removed along with the aneurysm.

FIG. 1b. Drawing showing main collateral blood supply to the intestine following ligation of the superior mesenteric artery.

A follow-up visit four weeks after operation revealed the patient to be in excellent condition. Shortly after leaving the hospital she had had alternate attacks of constipation and diarrhea for about one week, but these symptoms gradually subsided without treatment. All pain, both abdominal and lumbar which she had experienced prior to operation, had disappeared.

The patient was then referred to Dr. James A. Greene for further medical observation and care. When examined by him on July 28, 1950, whe was complaining of increasing shortness of breath and some nocturnal dyspnea. There was evidence of slight hypertension, the blood pressure at this time being 150/110. Treatment consisted of restricted sodium diet and digitalization.

In February 1951, while in Florida a recurrent episode of subacute bacterial endocarditis apparently developed but it responded satisfactorily to a two weeks' course of penicillin therapy.

When last observed on Oct. 6, 1952, almost three and one half years following resection of the aneyrysm, she was complaining of headache, dyspnea, excessive fatigability and slight ankle edema for about two months. Moderately advanced hypertensive fundi were noted and the blood pressure was 160/115. Dr. Don W. Chapman, who saw the patient in consultation at this time, expressed the opinion that the findings suggested the presence of aortic stenosis and mitral stenosis and insufficiency. Treatment was accordingly instituted with a satisfactory response.

FIG. 2. Photograph of the specimen which was sectioned longitudinally revealing a fibrous sac 0.3 to 0.5 cm. in thickness. Part of the sac is filled with thrombi in various stages of organization. Notice the silk ligatures on the stumps of vessels which originate on the periphery of the aneurysm.

DISCUSSION

According to the published reports most cases of aneurysms of the superior mesenteric artery are mycotic, being associated with subacute bacterial endocarditis or septicemia. In the 65 collected cases including our own, 41 (63 per cent) were mycotic, 9 (14 per cent) were syphilitic and 15 (23 per cent) were unspecified. The etiologic importance of infection in the formation of these aneurysms has long been recognized. Indeed the term *mycotic* was adopted for this purpose by Osler[36] and Eppinger[14] well before the turn of the century. In their extensive review of this subject Stengel and Wolferth[49] summarized the pathogenesis of this type of aneurysmal formation under the following mechanisms: (1) by lodgement of infected emboli in the lumina or the vasa vasorum of vessels, (2) by settling of bacteria on the media of vessels or in the vasovasorum, and (3)

by continuity or contiguity of infection from the aortic or pulmonic valves. Most of the cases of mycotic aneurysms of the superior mesenteric artery, like ours, have been associated with left sided endocarditis. In a small proportion of cases, however, as emphasized by Revell[40] the lesion may be considered primary in that it is not associated with any demonstrable intravascular inflammatory focus. The organisms most frequently encountered are the nonhemolytic streptococcus, pneumococcus and staphyloccus, but occasionally gonococcus, the influenza bacillus and other organisms have been observed.

There appears to be some tendency for mycotic aneurysms to be multiple often involving different vessels widely separated. Thus more than one aneurysm was found in 49 of the 217 cases collected by Stengel and Wolferth.[49] This is further exemplified by Lewis and Schrager's[29] collected series of 97 mycotic aneurysms occurring in 65 patients. Multiple mycotic aneurysms involving the superior mesenteric artery have also been found in a few cases.[14, 21, 26, 38, 56]

Characteristically, mycotic aneurysms occur in relatively young persons, usually males. This is probably a reflection of the original infection which is prone to develop in such individuals. In Lewis and Schrager's[29] collected series of 57 cases of mycotic aneurysms 91 per cent occurred in patients under 40 years of age and almost three-fourths were males. Similarly, 88 per cent of Stengel and Wolferth's[49] series of 174 collected cases were under the age of 40 years and almost 70 per cent were males. In the 40 collected cases of aneurysms of the superior mesenteric artery including ours, in which these data were available, 70 per cent were under 40 years of age and 82 per cent were males.

The clinical manifestations of aneurysms of the superior mesenteric artery are somewhat variable, being latent in some instances and having a rapid onset in others. In most cases the patient has been under medical observation for the underlying disease, usually endocarditis or some other serious infection, before development of the aneurysm. Its onset is most commonly manifested by attacks of abdominal pain, which may be relatively mild and recurrent or sudden and severe occurring in paroxysms. The pain is usually referred to the umbilicus or epigastrium. This is soon followed by the appearance of an abdominal mass which is often tender and pulsatile. The rapid development of the mass following the first attack of abdominal pain, often within a few weeks, has been noted by several observers. In many cases, however, the manifestations were not sufficiently characteristic to indicate the diagnosis. Indeed, in the majority of reported cases the diagnosis was made at the postmortem table.

Although the clinical picture of these aneurysms is not characteristic, a review of the published cases suggests that in a patient with endocarditis the occurrence of epigastric pain associated with or followed by the development of an abdominal mass should arouse suspicion of a mycotic aneurysm. The presence of expansile pulsation in the tumor and a systolic bruit provide additional evidence for this diagnosis. The relative mobility of such a pulsatile tumor as described in our case, is further evidence of an aneurysm of the superior mesenteric artery.

The prognosis of these aneurysms has been extremely poor, as almost all the published cases have had a fatal termination. Death was caused by the under-

lying disease or by rupture of the aneurysm. As early as 1851, Koch[24] directed attention to the tendency of these aneurysms to rupture. In 50 cases of the collected series in which the cause of death could be ascertained, rupture occurred in 23 (46 per cent).

Treatment of mycotic aneurysms, including some form of surgical attack, has been generally unsatisfactory, in a large measure due to the inability to control the underlying systemic infection. With the development of more effective antimicrobial agents curative treatment by surgical means may be employed with a higher degree of success. The various procedures which may be used in the surgical treatment of these lesions have been previously reviewed.[7, 15]

As far as can be determined from a search of the literature, there has been no case of mycotic aneurysm of the superior mesenteric artery in which treatment was successful prior to the case reported here. Apparently Stevenson,[51] in 1895, was the first to employ some form of surgical attack in such an aneurysm. The procedure consisted of exposure of the aneurysm by laparotomy and the introduction of two yards of fine steel wire into the sac through a cannula. The patient died from hemorrhage 27 hours later. A somewhat similar procedure was employed in a patient operated upon by Dr. J. M. T. Finney, in 1898, who also used a galvanic current to induce thrombosis but with equally poor results, the patient dying 20 days postoperatively.[39] Exploratory laparotomy only was done in 3 cases.[2, 23, 46] In 1908, Stern[50] reported the first case in which extirpation of the aneurysm was performed. At the first operation on Jan. 19, 1906, a tumor, "the size of a small apple in the mesentery" was first considered to be an abscess of the mesenteric glands. Further dissection showed it to be filled with "old blood clots laid out like onion skin," the removal of which soon produced a "strong spurting of arterial blood from the mesenteric artery." The artery was doubly ligated and the cavity formed by the removal of the coagulum was closed after insertion of iodoform gauze strips. On March 2, 1906, 42 days after this procedure, the second operation was performed because of the development of another abdominal tumor. Exploration at this time revealed the tumor to be an aneurysm the size of a fist, arising in the root of the mesentery and partially involving the aorta. In an effort to remove the serosa from the aneurysm the sac was torn and severe hemorrhage ensued. This was finally controlled but the patient died immediately after the operation.

In 1923, Kolin[25] reported the next case in which extirpation of an aneurysm of the superior mesenteric artery was done. The aneurysm, which in this case was about the size of a "hen's egg," was lying in the root of the mesentery. After it was freed from the surrounding structures and a few vessels connected with the sac but showing no pulsations were ligated, the stem of the aneurysm was ligated and it was removed in toto. As in our case, it was necessary to ligate and resect a segment of the superior mesenteric vein which was intimately adherent to the posterior wall of the aneurysm. The patient died 17 hours after operation apparently of cardiac failure. Necropsy revealed evidence of recent and old endocarditis of the mitral and semilunar valves and aortic and mitral stenosis and insufficiency.

The major technical consideration in the surgical treatment of aneurysm of the

superior mesenteric artery is concerned with the potential ischemic consequences of occlusion of this vessel. It has long been known that sudden occlusion of this artery or its major branches is followed by gangrene of the intestine.[53] It has also been demonstrated that an extensive collateral circulation sufficient to maintain viability and function of the intestine can take place even when there is complete occlusion of the mesenteric vessels, providing the occlusive process develops gradually.[4, 27] A number of cases has been reported in which at autopsy the superior mesenteric artery and its branches were found to be represented by fibrous cords, the patients having died of other causes.[5, 22, 25, 52, 55]

For many years the early experimental observations of Litten[30] that the mesenteric arteries and their branches behaved physiologically as end-arteries prevailed. Subsequent studies by Cokkinis[6] showed that these conclusions should be modified. The latter investigator clearly demonstrated that "the collateral circulation with the mesentery itself, up to and including the terminal row of arcades, is very free, and occlusion of quite large vessels fails to prevent injections at fractional pressures reaching every part of their territory." More recently experimental studies by a number of workers have shown that the prevention of thrombosis by the use of anticoagulant drugs and of bacterial proliferation by such antibacterial agents as sulfasuxidine and streptomycin are important factors in maintaining adequate circulation and viability of the intestine following acute occlusion of the superior mesenteric vessels.[11, 35, 43] On the basis of these observations it would appear that the normal collateral communications of the main branches of the superior mesenteric artery may be adequate to maintain a viable blood supply if occlusion by ligation is produced within this vascular bed and providing the occlusive process does not spead by thrombosis, for example, to involve the vascular bed distal to the point of ligation.

The external anastomoses of the superior mesenteric artery are derived primarily from the communication of the superior pancreaticoduodenal branch of the gastroduodenal artery and the inferior pancreaticoduodenal branch of the superior mesenteric artery and the communication of the left colic branch of the inferior mesenteric artery with the midcolic branch of the superior mesenteric artery (fig. 1). Additional collateral circulation may also be provided by communications between branches of the last dorsal and lumbar arteries and those of the mesenteric vessels.

It is apparent from these observations that a functional collateral blood flow is available to meet the needs of the vascular bed supplied by the superior mesenteric artery. This collateral blood flow is capable of meeting the physiologic requirements only if the occlusive process in the superior mesenteric artery takes place gradually to permit sufficient time for the collateral vessels to adjust to these needs. Both Kolin[25] and Stern[50] recognized these factors of compensability in the vascular requirements and collateral blood flow of the mesenteric arterial bed. They emphasized the fact that in their cases ligation of the superior mesenteric artery above the aneurysm caused no ischemic changes in the circulation of the intestine and reasonably assumed that this may be explained on the basis that the aneurysm had acted as a gradually occlusive agent, reducing the blood

pressure and slowly diminishing the blood flow in the mesenteric vessels distal to the aneurysm, thus producing the stimulus for a gradually developing collateral blood supply. The results obtained in our case lend additional evidence in support of this assumption.

Because the superior mesenteric vein is often intimately adherent to the aneurysm in these cases consideration must be given to its ligation in excision of the sac. This was necessary in the case reported by Kolin[25] as well as in our case. While a few cases of successful ligation of the superior mesenteric vein for injury of this vessel have been recorded,[34, 44, 57] the consequences of acute occlusion of this vessel are generally considered to be as hazardous as those following occlusion of the artery.[12] It would appear, too, that the factors influencing adequacy of the circulation and collateral blood flow following occlusion of the artery are equally applicable to the vein. A possible means of avoiding ligation of the vein when it cannot be safely freed from the sac is to excise all of the aneurysm except that part of the wall of the sac which is intimately adherent to the vein.

From these experimental and clinical observations it may be concluded that ligation of the superior mesenteric artery as an essential step in the resection of an aneurysm of this vessel can be safely done. The result obtained in our case also leads us to conclude that resection of these aneurysms is the procedure of choice and can be successfully accomplished provided proper supportive measures are instituted and the underlying infectious disease is controlled. With the more effective antimicrobial agents that are now available preliminary control of the infection should readily permit institution of successful surgical treatment of these aneurysms.

SUMMARY

Aneurysm of the superior mesenteric artery is rare and in the majority of cases the diagnosis is made at postmortem examination.

A case is reported of a 27 year old woman with compensated rheumatic heart disease, arrested subacute bacterial endocarditis, and mycotic aneurysm of the superior mesenteric artery. Extirpation of the aneurysm with concomitant ligation of the mesenteric artery and vein was successful and all symptoms from the lesion were relieved.

In the 65 collected cases including our own 41 (63 per cent) were mycotic, 9 (14 per cent) were syphilitic and 15 (23 per cent) were unspecified.

The possibility of aneurysm of the superior mesenteric artery should be strongly considered in any patient with a history of endocarditis and the occurrence of epigastric pain associated with the appearance of a pulsatile and highly mobile mass in the upper abdomen. In our patient the diagnosis was made on this basis before operation.

In a review of the literature no other case of successful resection of such an aneurysm was found. Ligation of the superior mesenteric artery and vein can be safely done in instances where gradual vascular occlusion has stimulated the development of collateral arterial and venous channels to the involved viscera. Extirpation of the aneurysm is recommended in such cases in preference to other methods of surgical correction.

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INFECTED COMPOUND FRACTURES OF THE ANKLE

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Compound fractures of the ankle are almost invariably fractures of the so-called Pott's type. The mechanism of injury is forced abduction or eversion of the foot. The compound wound is transverse and placed medially. The presenting bone in the wound is the proximal portion of the medial malleolus at the level of the joint line. Contamination of the joint is often *street dirt* as the bone actually comes in contact with the street or ground. When the displacement or dislocation of the foot is reduced, the contaminated joint is then sealed tightly. This dislocation or displacement is most easily reduced and is usually done by the person rendering first aid and applying the splint. Notwithstanding the marked displacement vascular injury is rare.

On cross section of the ankle it is found to be "H" shaped. Recesses are found in both the horizontal and vertical planes, the center of which is the astragalus. Therefore, to debride adequately or explore this joint two incisions are necessary, *e.g.*, extension of the compound wound medially and a lateral incision.

Infection of this joint is not common, but when it does occur it is most disabling. The problems are: 1. Difficulty in establishing adequate drainage. 2. Lack of soft tissue coverage, *e.g.*, the joint is entirely subcutaneous on three sides. 3. Infection of cancellous bone. 4. Circulatory disturbances with secondary skin changes due to venous incompetency are common in the lower extremities. 5. Absence of excess skin for shifting flaps.

Once infection is established in the ankle it is impossible to drain all recesses surgically. Drains are of little help. If the medial aspect of the joint is saucerized there is no soft tissue such as muscle to place in the defect so that one may do a split thickness graft. Split thickness grafts applied to bone in this area are doomed to failure. Excess skin locally is not available for shifting a full thickness flap. We are familiar with infections of cancellous bone and their chronicity and failure to form definite sequestra. Therefore, attempts at removal of involved bone leave an unstable, infected joint with a gap of 2 or more inches at the ankle joint.

The sequellae of repeated cast changes and inability to bear weight over a period of months are familiar to all. In the case of the compound wound infected ankle, persistent swelling, clawing of the toes, and pain are most common. Osteoporosis of the small bones of the foot occurs early and is a further complicating factor. As in other joints, antibiotics are of little value in the established infections. The infection is often a mixed one and the organisms become rapidly resistant to the antibiotics.

At this point it is important to consider the outlook of the patient. He rapidly

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becomes discouraged. Most often the patient is in his *thirties* and though the draining wound is small it persists and he is not able to support his family. The more fortunate, after months, may return to work to lose time again because of pain and recurrence of drainage. The patient may and often does demand ampu-

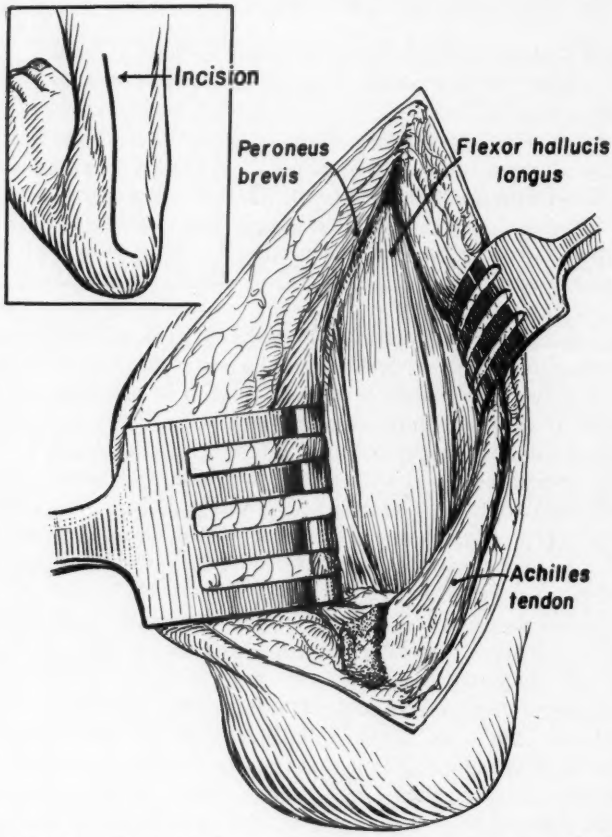

FIG. 1. (a) Incision; (b) Interval on fibula between peroneus brevis and flexor hallucis longus.

tation. The physician himself becomes discouraged as each step seems to lead nowhere.

With the above background of discouragement the author became interested in this problem. He reasoned on the basis of the Campbell posterior ankle fusion which was used for tuberculosis. Also successful fusion of other infected joints, *e.g.*, the hips, results in a useful extremity. It would seem that this principle would be applicable to the ankle.

Four cases have been treated in a period of two years, all of which are now

more than one year since operation. Drainage was present from the medial wound at the time of operation in all 4 cases. All patients had agreed to amputation should the procedure fail. No amputation in the group has been necessary and all of the patients are ambulatory without support. The medial wound has healed and remained healed in all cases. There have been no surgical infections. In 1 case roentgenograms made during forced flexion and extension, indicate that

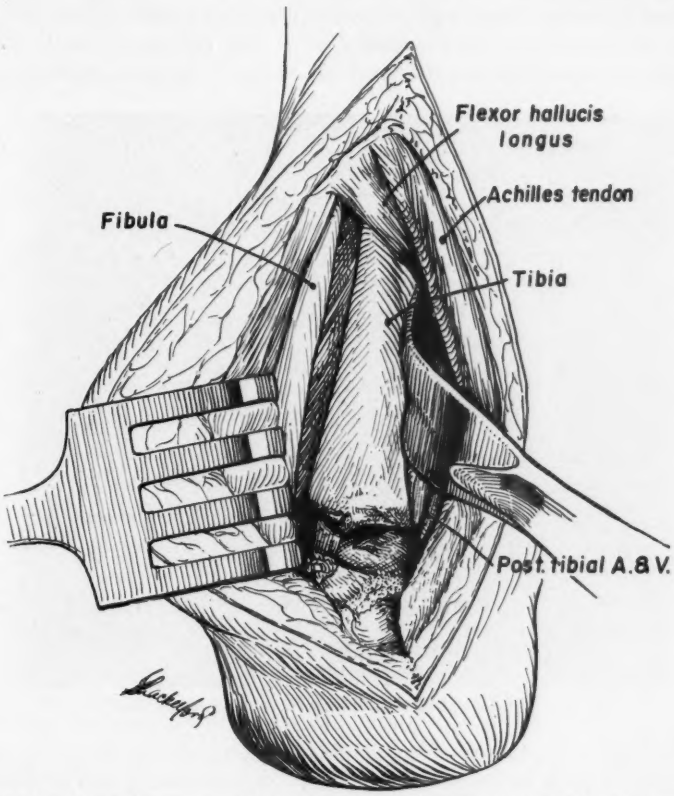

FIG. 2. Demonstrates exposure of posterior aspect of tibia and os calcis with intervening capsules.

bony fusion is not solid though there is a strong fibrous ankylosis. The patient is ambulatory without support and engaged in productive work. His compound wound has never shown any evidence of recurrence of drainage. This would seem to indicate that solid bony fusion is not necessary, but rigid ankylosis is the important factor in controlling the infection, drainage, and pain.

The patient is transfused, if necessary, prior to operation to assure normal hemoglobin and red blood cell count. Phisodern scrubs of the skin of the lower

leg and foot are carried out twice daily by the patient. Sensitivity of organisms is determined and the antibiotic or antibiotics preoperatively are begun as indicated. A tourniquet is applied. The operative procedure is carried out with the patient in the prone position. One posterior iliac crest is prepared for the donor area. The compound wound is carefully prepared and draped outside of the operative field. The iliac graft is taken first and the graft wound closed. Only long cancellous strips are taken from the ilium.

A posterolateral incision is made extending along the tendo-achilles (fig. 1) onto the heel and curving slightly medially. The heel cord is reflected by sharp dissection incompletely from the os calcis. The interval between the flexor hallucis

FIG. 3. Medial draining compound wound

longus and peroneus brevis on the fibula is easily identified. The flexor hallucis is removed from its origin on the fibula by sharp dissection and reflected as a flap subperiosteally from the dorsum of the tibia (fig. 2). The neurovascular bundle lies in the protective covering of the flexor hallucis. The fat interval between the heel cord and the ankle and subastragalar joints is removed by rongeurs. The dorsal capsules of the joints are easily identified but not opened. By means of a curved gouge, bone taken from the tibia and os calcis is interlaced across the joints. The cancellous strips from the ilium are added. In no case was frank pus or infected granulation tissue encountered either of bone or soft tissue in this approach. The muscle flap of the flexor hallucis longus is then sutured to the fibula over the bone grafts. As good relationship of foot to the lower leg is obtained as possible without opening the joints. A high thigh cast is applied with

the knee in flexion. This is worn for eight weeks and then a short leg walking cast is applied and worn for another four to six weeks. The surgical wounds have all healed per primum and the compound wound was healed at the first cast change and remained healed.

A typical case of the series is as follows: L. J., a 31 year old Latin American man sustained a compound "Pott's" type of fracture of the right ankle on Sep. 22, 1950. The compound wound was debrided and placed in a long leg cast for two and one-half months. He was then allowed up on crutches. When seen on the Orthopedic Service on April 6, 1951 there had been persistent drainage since the accident and the patient had borne no weight on the extremity.

FIG. 4. Roentgenograms, April 1951. Note destruction of bone, irregularity of ankle joint, and spotty decalcification of the tarsal bones.

Examination revealed a well developed Latin American man of stated age. The entire foot was swollen and edematous. On the medical aspect of the ankle there was a transverse draining wound 4 by 1 cm. (fig. 3). The base of the wound was bone. Marked limitation of motion of the toes was present with tendency to claw formation. The foot was held in 10 degrees of equinus and there was only a jog of ankle motion possible which was painful. The heel could be inverted 10 degrees, but no eversion was possible.

Roentgenograms, (fig. 4). Anteroposterior, lateral and oblique roentgenograms of the right ankle revealed extensive osteoporosis of the foot and ankle. There was apparent sequestration of the entire medial malleolus. An old healed fracture of the distal third of the fibula and narrowing of the ankle was present.

FIG. 5. Healed compound wound September 1951

FIG. 6. Forced dorsiflexion and plantar flexion of the foot demonstrating bony fusion August 1952. Compare bone density of tarsals with that of figure 4.

Laboratory data. Culture of wound revealed nonhemolytic staphlococcus aureus organisms which are moderately sensitive to penicillin.

Course in hospital. On May 9, 1951 a posterior ankle fusion was performed

using extra autogenous cancellous bone from the iliac crest as described under technic. The operative wound healed per primum. A walking cast was applied on June 26, 1951 and all wounds were healed (fig. 5). In September 1951 he was placed in a short leg brace. He then returned to work as a plumber, working eight hours while standing on his feet. He has last seen in the clinic Aug. 26, 1952. He had no complaints and there was solid bony fusion of the ankle (fig. 6). There has been no drainage from any wound for over one year.

SUMMARY

An approach to the treatment of infected draining compound fractures of the ankle is presented. There were 4 cases in this group, all treated by posterior extra-articular tibio-calcaneal fusion. All compound wounds were healed at the first plaster change and have remained healed for one year.

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